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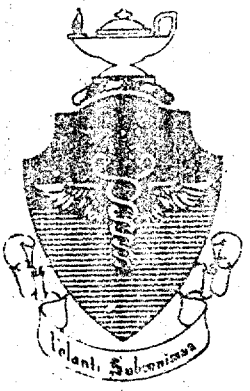
AN EPIDEMIOLOGIC INVESTIGATION OF HEALTH EFFECTS IN AIR FORCE PERSONNEL FOLLOWING EXPOSURE TO HERBICIDES

BASELINE MORTALITY STUDY RESULTS

30 JUNE 1983



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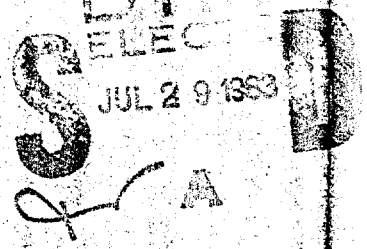

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In 1979 the United States Air Force (USAF) made the commitment to Congress and to the White House to conduct an epidemiologic study of the possible health effects from chemical exposure in Air Force personnel who conducted aerial herbicide dissemination missions in Vietnam (Operation RANCH HAND). The purpose of this epidemiologic investigation is to determine whether long-term health effects exist and can be attributed to occupational exposure to herbicides. This study uses a matched cohort design in a nonconcurrent prospective setting, incorporating mortality, morbidity, and follow-up studies.

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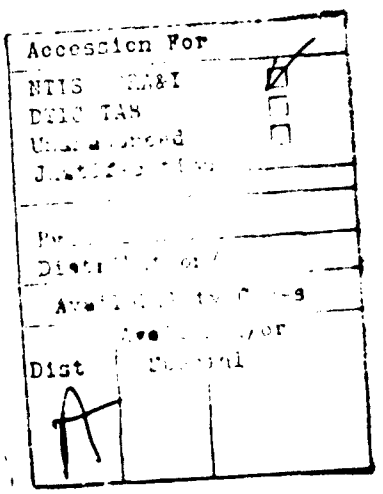
The purpose of this report is to present the baseline mortality study results. As of December 31, 1982, 50 Ranch Hand and 250 comparison subjects had died (certified on/before April 27, 1983). Data analysis showed that the mortality experience of the Ranch Hand group is nearly identical to that of this comparison group. However, this mortality report can in no way be regarded as conclusively negative since the study population may not yet have reached the latency period. Subsequent mortality reports will include additional anaylses and will be updated annually for the next 20 years.



EXECUTIVE SUMMARY
Baseline Mortality Study

The Ranch Hand II epidemiologic study uses a matched cohort design in a nonconcurrent prospective setting, incorporating mortality, morbidity, and follow-up studies. The purpose of this report is to present the baseline mortality study results.

Since 1979, a detailed population ascertainment process has enumerated a total of 1269 Ranch Hand personnel who served in Vietnam during the period of 1962-1971. As described in the protocol, this total is believed to comprise the entire exposed study population. The eligibility of each Ranch Hander was verified by a hand review of his personnel record. A comparison group was formed by identifying all individuals assigned to selected Air Force organizational units with a mission of flying cargo to, from, and in Vietnam during the same period. All Ranch Hand and comparison subjects designated as killed in action were removed from the study population. By a computerized nearest neighbor selection process, up to 10 comparison individuals were matched to each Ranch Hander by job category, race, and age to the closest month of birth. A hand record review of the matched comparison sets revealed that on the average, 8.2 comparison individuals were fully suitable for study. From each matched comparison set, five individuals were randomly selected for the mortality study, yielding a 1:5 design. Every Ranch Hander and his set of comparisons will be the subjects of annual mortality updates throughout the entire 20 years of the follow-up study so that emerging mortality patterns or disease clusters may be detected with maximal sensitivity. Each living Ranch Hander and his first and willing comparison match were selected to participate in a comprehensive physical examination and an in-home interview; the results of this study will be presented in a subsequent report in late 1983.

A mortality determination on 1,247 Ranch Handers and 6,171 comparison subjects was made, sequentially using the data sources of the Air Force, Veterans Administration, Social Security Administration, Internal Revenue Service, and personal contact efforts. As of December 31, 1982, 50 Ranch Hand and 250 comparison subjects had died (certified on/before April 27, 1983). Death certificates were obtained on all 300 deceased subjects and were coded by an Air Force nosologist (ICD, 9th ED). All codings were verified by the National Center for Health Statistics. Autopsy results are currently being sought for future analyses.

Statistical analyses of noncause specific death emphasized survival curve estimates, linear rank procedures, relative risk estimates, and standardized mortality ratios (SMRs). Cause specific analyses were limited to relative risk estimates because of small cell sizes. In addition to these approaches, three other data bases were contrasted to the Ranch Hand population, where possible; the 1978 US White Male Mortality experience, the 1978 Department of Defense (DoD) Nondisability Retired Life Table, and the mortality experience of the West Point Class of 1966. These additional comparison groups have substantial comparability or sample size limitations, rendering conclusions to the weakest order. Analyses with these "external" comparison groups were accomplished to crudely define the healthy worker effect and to determine if the Ranch Hand group mortality was drastically out of line with that of other military populations.

Data analysis showed that the mortality experience of the Ranch Hand group is nearly identical to that of the comparison group. Analyses showed that officers are living longer than enlisted personnel in both Ranch Hand and comparison groups. This difference between officers and enlisted personnel was statistically significant in the comparison group whereas it was not in the Ranch Hand cohort. A contrast of the Ranch Hand and comparison group to the 1978 DoD Life Table showed significantly less mortality for Ranch Hand officers, comparison officers and comparison enlisted men, however, there was not a statistically significant favorable mortality rate for Ranch Hand enlisted personnel. This pattern of mortality was also seen in a contrast of the Ranch Hand and comparison groups to the 1978 U.S. white male mortality experience. That is, highly favorable mortality differentials for Ranch Hand officers, comparison officers and comparison enlisted personnel were observed, but not for Ranch Hand enlisted. This trend is consistent with the self perceptions of differential herbicide exposures reported by many of the Ranch Hand subjects. The reason(s) for these observations are speculative at present, but may include the related items of sample size, socioeconomic differences, access to medical care, and health education and possible herbicide effects. Cause specific analyses were statistically nonsignificant. The Ranch Handers showed a relative paucity of overall cancer but an excess of digestive disorder deaths, both statistically nonsignificant. No soft tissue sarcoma deaths were detected in either group. Analyses of both the Ranch Hand and the comparison groups to the 1978 US White male mortality experience showed highly significant favorable findings. Most of these differences are speculatively attributed to the healthy worker effect. A contrast of the Ranch Hand and comparison groups to the 1978 DoD Life Table showed significantly less mortality for Ranch Hand officers and comparison officers and enlisted men. The West Point comparison showed nonsignificant SMRs of 0.530 and 0.778 for the Ranch Hand officers and the comparison group officers, respectively. Overall, the limitations of the statistical power calculations in most of these analyses were substantial in most analyses due to 1) the low mortality rate (4%) in the Ranch Hand and comparison groups to date, 2) the inherently small group of Ranch Handers (as described in the study protocol), and 3) the observed relative risks which approached unity in most categories.

This baseline mortality report can in no way be regarded as conclusively negative because this small, young, and relatively healthy cohort may not have yet reached the latency period wherein attributable fatal disease might be expected and detected within limited power boundaries of this study. Future commitments for the annual mortality updates include detailed covariate analyses for disease risk factors, herbicide exposure, and confounding industrial chemical exposures. Further, subsequent morbidity reports will include full spectrum, disease specific analyses, e.g., cancer (fatal, ongoing, cured) in an effort to enhance study sensitivity to emerging herbicide effects, if they occur.

PREFACE

In October 1978, the United States Air Force (USAF) Surgeon General made the commitment to the Congress and to the White House to conduct an epidemiologic study of the possible adverse health effects arising from the herbicide exposure of Air Force personnel who conducted aerial dissemination missions in Vietnam (Operation Ranch Hand). The purpose of this epidemiologic investigation is to determine whether long-term adverse health effects exist and whether they can be attributed to occupational exposure to herbicides and their contaminants. The study protocol (1) for this effort incorporates a matched cohort design placed in a nonconcurrent prospective setting. The study approach includes mortality, morbidity, and follow-up elements linked tightly in time, in order to produce the most data in the shortest period of time. The study addresses the question: Has there been, or are there currently, or will there be any adverse health effects among former Ranch Hand personnel caused by repeated occupational exposure to 2,4,5-T containing herbicides and the contaminant, TCDD? At the request of the Principal Investigators (see Appendix I) the study protocol was extensively and independently peer reviewed. The review agencies included: The University of Texas School of Public Health, Houston Texas; the USAF Scientific Advisory Board; the Armed Forces Epidemiological Board; and the National Research Council of the National Academy of Sciences. In 1980, the Science Panel of the Agent Orange Working Group was created as an additional peer review agency. This group, redesignated as the Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants, has consented to the oversight responsibility of the Ranch Hand study and continues to monitor the conduct of this epidemiologic investigation (see Appendix II). The approved and official protocol for this effort is available to the public through the National Technical Information Services, 5285 Port Royal Road, Springfield, Virginia 22161.

The Ranch Hand II Study protocol heralds the suboptimal statistical power of the mortality study. The mortality study was motivated by the desire to use a full spectrum epidemiologic approach to the herbicide question. Additionally, the investigators were scientifically obliged to pursue the mortality study because of previous and emerging studies (some with small sample sizes) which suggested the possibility of a soft tissue sarcoma end point (2,3,4). Within the inherent sample size limitation of the Ranch Hand population, detection of such a rare condition will be missed unless there is marked case clustering and correspondingly high relative risks.

Also, because of sample size limitations as well as the myriad of proposed clinical end points, a case-control design was not entertained. The investigators have attempted to enhance statistical power and analytic sensitivity where possible by using 1) a large comparison group, 2) precise matching procedures, 3) annual mortality updates, 4) mortality-morbidity linkages, 5) a lengthy follow-up study, 6) external comparison groups, and 7) state-of-the-art statistical methodology. A final assessment of overall mortality must necessarily await substantially more data and covariate approaches to identify and isolate unusual emerging mortality patterns, if they occur.

This report is primarily directed to individuals with statistical and epidemiologic backgrounds. It also assumes that the reader has a familiarity with the herbicide/dioxin issue and a detailed knowledge of the protocol of the Air Force study. In the interest of brevity, the reader is referred to the protocol published as US Air Force School of Aerospace Medicine Technical Report 82-44.

Chapter I

THE MORTALITY STUDY DESIGN

1. The Study Population

The exposed study population, termed "Ranch Hand", was defined as those individuals who were formally assigned to the USAF organizations responsible for the aerial dissemination of herbicides and insecticides in the Republic of Vietnam from 1962 to 1971. These individuals were identified from historical data sources at the National Personnel Records Center (NPRC), St. Louis, Missouri and the USAF Human Resources Laboratory, Brooks Air Force Base, Texas. A total of 1,269 Ranch Hand personnel were eventually identified through this process. The comparison population was defined as those individuals who were assigned to a variety of cargo mission organizations throughout Southeast Asia during the same time period. Cargo mission aircrew members and support personnel were selected because of sufficient population size, similar training and military background experiences, and psychologic similarities to the Ranch Hand group. The comparison population was not occupationally exposed to herbicides or insecticides in the Republic of Vietnam. Identification of this population was completed using the same historical data sources as were used with the Ranch Hand population; 24,971 individuals were so identified. In preparation for matching the study and comparison populations, all subjects killed in action (KIA) were removed from the data base. The rationale for this action is the assumption that combat death in the Ranch Hand group was not caused by the immediate effects of herbicide exposure; KIA's were removed from the comparison group for comparability purposes. A KIA analysis will be performed in a subsequent report. The Ranch Hand KIA subgroup, numbering 22 individuals, although not matched, was maintained in the data base but was deleted from the mortality analysis, leaving 1247 Ranch Hand subjects.

The Ranch Hand population was matched to the comparison population with an iterative nearest-neighbor computer program (1). Up to 10 comparison subjects were matched to each Ranch Hander by year of birth, race (Black versus non-Black), and occupational category (officer pilot, navigator and other; enlisted flight engineer and other), thus creating matched sets of one study subject and up to 10 comparison subjects. All subjects are males. The mean age of the study subjects is 45 years.

Following the original match, the majority of Ranch Handers had 10 comparisons. The exceptions were the group of non-Black pilots who had a mean of only 9.5 comparisons per exposed subject due to the extreme ages of several individuals, and the strata of Black pilots and other Black officers who only had means of 2.7 and 5.0, respectively. In December 1981, the USAF Principal Investigators learned that several morbidity study comparison subjects had reported no experience in Southeast Asia, suggesting that overselection of the comparison population had occurred (1). Manual review of the comparison subjects' military personnel records revealed that 18 percent of the 12,193 comparison individuals in the original match were ineligible for study. The inadvertent inclusion of several non-Southeast Asia organizations resulted in the selection of these inappropriate individuals. These ineligible subjects were found to be randomly distributed throughout the matched sets and were removed from the study. Following the removal of the

ineligible subjects, the study was reduced to a 1:8 design. Also during this period, five Ranch Hand subjects were identified through personnel record sources and Veterans Administration Education Benefits and Financial Records. These five individuals had not been identified earlier because the majority of their military personnel records had been destroyed in a fire at the NPRC in St. Louis. Three of these five were newly found Ranch Handers and two were comparisons subsequently identified as Ranch Handers. No attempt was made to match comparisons to these five new Ranch Handers. During the removal of ineligible subjects, one Ranch Hander, a Black officer pilot, lost his only comparison and remains unmatched, giving a total of six unmatched Ranch Handers. All six of these unmatched Ranch Handers are included in the morbidity and mortality studies. They were used in the analyses where appropriate, in order to improve statistical power.

2. The Mortality Population

Five comparisons per exposed subject were considered more than adequate for mortality analyses; this estimate has recently been verified under a multiplicative model by Breslow, et al. (5). Up to five comparisons in each matched set, were identified from the 1:8 cohort as the mortality comparisons. Since the positions of the individuals in the matched sets had already been randomized in the data file, the selection of the first five positions in each matched set array for membership in the mortality comparison resulted in a random selection of the mortality comparison cohort. If a Ranch Hander had at least one but no more than five comparisons after removal of the ineligibles, then all of his matched set were used in the mortality component of this study. The mortality population is, therefore, defined as the 1241 matched Ranch Handers and their randomly chosen mortality comparisons (6171 individuals) and the six unmatched Ranch Handers. Table 1 summarizes the mortality population by occupational category and race. Here, and elsewhere in this report, non-Black is defined as Caucasian, Mexican or Oriental.

Table 1

MORTALITY POPULATION SUMMARY BY OCCUPATION AND RACE

Occupation, Race	Counts	
	Ranch Hand	Comparison
Officer-Pilot, Non-Black	349	1740
Officer-Pilot, Black	6	13
Officer-Navigator, Non-Black	80	390
Officer-Navigator, Black	2	10
Officer-Other, Non-Black	25	123
Officer-Other, Black	1	2
Enlisted-Flt Eng, Non-Black	189	935
Enlisted-Flt Eng, Black	15	75
Enlisted-Other, Non-Black	529	2628
Enlisted-Other, Black	52	255
	1247	6171

The overall match ratio, 6171/1247=4.95, reflects the lack of suitable controls in some strata, the subsequent removal of ineligible comparisons and the addition of five unmatched Ranch Handers. A detailed description of the matching results is given in Appendix III.

Those Ranch Handers having fewer than five matched mortality controls are summarized in Table 2.

Table 2

RANCH HAND SUBJECTS WITH LESS THAN FIVE COMPARISON SUBJECTS

Occupation, Race	Counts		Notes
	Ranch Hand	Comparisons[3]	
Officer-Pilot, Non-Black	1	2	1
	1	3	1
Officer-Pilot, Black	1	0	1
	1	1	1
	2	2	1
	1	3	1
Officer-Navigator, Non-Black	2	0	2
Officer-Other, Non-Black	2	4	1
Officer-Other, Black	1	2	1
Enlisted-Flt Eng, Non-Black	2	0	2
Enlisted-Other, Non-Black	12	4	1
Enlisted-Other, Black	1	0	2
	27		

Note 1. Lack of suitable comparison subject or loss due to ineligibility.
Note 2. New Ranch Hander, no attempt to match.
Note 3. Comparisons per Ranch Hander

Chapter II

THE MORTALITY DETERMINATION PROCESS

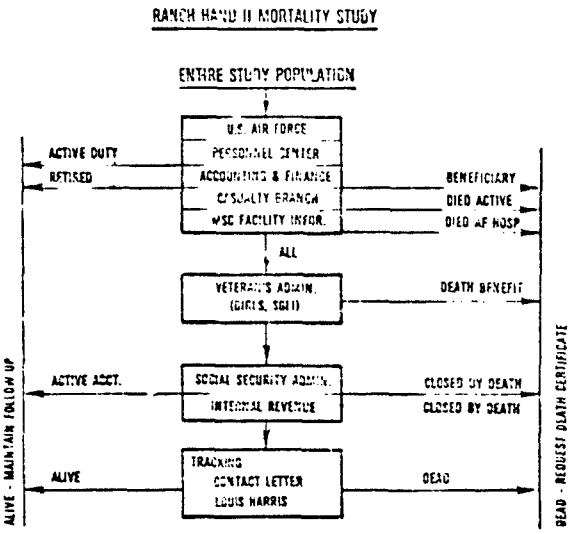
1. Introduction

The mortality status of the Ranch Hand group and their mortality comparisons are, and will continue to be, ascertained using four major data sources: USAF, Veterans Administration (VA), other Governmental and morbidity population tracking. The mortality determination process using these data sources is presented in Figure 1.

Figure 1.

RANCH HAND II

MORTALITY DETERMINATION ALGORITHM



The entire study population was matched or checked against the first three sections of this algorithm while only the morbidity population was contacted and tracked. A description of the data sources within the algorithm follows.

2. United States Air Force Data Sources

The USAF data sources include the USAF Military Personnel Center (MPC) records, the USAF Accounting and Finance Center records, and the USAF Medical

Service Center Facility Use Data. The USAF MPC records include the individual's military personnel record and the data accumulated by the Casualty Branch of the MPC. Individual military personnel records are created at the time of induction into the USAF, and reflect a chronological history of the individual's military career. Epidemiologically, these records are an invaluable data source as they can be used for the development of occupational histories, identification of race, sex, and date of birth as well as for location of personnel, and for determining vital status. Hard copy records of these data are maintained at the individual's base of assignment while on active duty; a computer copy of these records is maintained at the USAF military personnel center, Randolph AFB, Texas. Following retirement and/or separation from the USAF, these records are forwarded to the National Personnel Records Center (NPRC), St Louis, Missouri, the record repository for all military personnel records. They are indexed by Social Security Account Number or Air Force Serial Number at the NPRC. If an individual should die while on active duty, after retirement, or within 120 days of separation from active duty, it is the responsibility of the Casualty Branch of the USAF Military Personnel Center to update the hard copy military personnel record and the MPC computer data base and to inform the USAF Accounting and Finance Center of this fact. At the same time, USAF MPC personnel initiate a copy of the USAF Form 1312, Report of Retired Casualty, or Department of Defense DD Form 1300, Report of Casualty. The selection of the appropriate form is based on the current status of the individual concerned. The DD Form 1300 also clarifies an individual's casualty status which can be either battle or nonbattle. Copies of the appropriate death form are sent to appropriate agencies while the original is placed in the individual's military personnel record.

Since the initial review of military personnel records, a system has been established with the Casualty Branch of the Military Personnel Center wherein all active duty and retired death forms are forwarded monthly to the Occupational Epidemiology Section of the USAF School of Aerospace Medicine Epidemiology Division. In this way, the mortality status of all active duty and retired study subjects is systematically determined on a continuing basis.

The USAF Accounting and Finance Center data base was used as a resource to update individual Air Force serial numbers to Social Security numbers. The Social Security number is required for all other aspects of the mortality algorithm.

The Air Force Medical Service Center (AFMSC) Facility Use Data is a computer data base containing information regarding all active duty and retired deaths that occur in Department of Defense (DOD) Medical Facilities. This data base identified no additional deaths in the mortality population, but did verify the deaths known to have occurred in DOD hospitals.

In addition to the USAF data bases, the Ranch Hand Association, a reunion association of approximately 850 Ranch Handers, has contributed to the success of this study. This group has assisted the Principal Investigators in the ascertainment of the exposed population, and in the determination of the current location and the mortality status of the group. The association contacts all of its members yearly through newsletters and provides updated information to the Air Force investigators.

3. Veterans Administration Death Beneficiary Identification and Record Location Subsystem

The Beneficiary Identification and Record Locator Subsystem (BIRLS) is a Veterans Administration data base generated by the Veterans Administration for determination of funeral allowance. If the family of the deceased informs the funeral director that the deceased served in the US military, the funeral director submits the required data to the Veterans Administration. In January 1981, August 1982,and January 1983,the BIRLS data base was searched for Ranch Hand and comparison deaths. In addition to these searches, the Department for Veterans Benefits, Veterans Administration, coordinated the gathering of death certificates from VA regional offices.

4. Other Governmental Data Sources

A. Internal Revenue Service

Public Law 96-126, Section 502, 28 November 1979, authorized the use of Internal Revenue Service (IRS) addresses for individuals who had been exposed to occupational hazards in order to determine the status of their health. The National Institute for Occupational Safety and Health (NIOSH) coordinated the USAF requests for these IRS addresses. This system is based on the address shown on individual tax returns and is corrected once a year. The addresses are verified by NIOSH through use of a post card mailed to the post office responsible for the individual's mail delivery. NIOSH assumes that the individual is alive if he files a tax return and if the verification scheme confirms his address for mail delivery. The IRS assumes an individual is dead if the individual is so reported on a joint tax return. The IRS data base search provides an incomplete mortality determination, however, since absence of an individual tax return does not necessarily imply death of that individual.

B. Social Security Administration

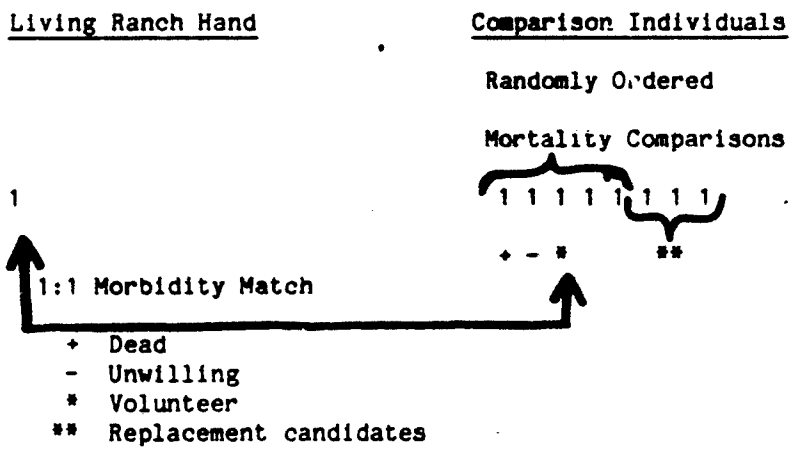
The Social Security Administration (SSA) is a source of mortality information based on data maintained by the Office of Renumeration and Earnings. The basis for this data is employer-reported earnings. The SSA assumes that an individual is living if there is no indication of death on the individuals record and earnings are recorded for the last calendar year or retirement, disability, black lung or supplemental security income payments are being made. The SSA did inform us that they do not conduct an exhaustive search, and all deaths are not necessarily reported to SSA. Therefore, this mortality information may not be complete.

5. Morbidity Population Tracking

Individual tracking techniques apply only to the morbidity population, defined as those selected and compliant to questionnaire. The morbidity population for this effort is defined as all Ranch Handers and their morbidity comparisons. The morbidity comparisons are, in general, also mortality comparisons. The selection procedure for the morbidity study is presented in Figure 2.

Figure 2.

SELECTION PROCEDURE FOR THE QUESTIONNAIRE, PHYSICAL EXAMINATION, AND FOLLOW-UP STUDY



\+ Dead
\- Unwilling
* Volunteer
** Replacement candidates

In this figure, the first randomly ordered comparison was found to be dead. The second was contacted but was unwilling to participate and the third volunteered to participate in the questionnaire component of the morbidity effort. This contacting process for the morbidity effort was the final step in the baseline mortality determination. The original contact was made by certified mail. Each Ranch Hander and a random living comparison were sent an introductory letter and fact sheet signed by the USAF Surgeon General. A Louis Harris and Associates (LHA) interviewer then accomplished an in-home interview.

LHA identified two Ranch Handers and nine comparisons who could not be located. All eleven unlocatable subjects were assumed living and remain included in the mortality study.

6. Receipt and Coding of Death Certificates

Death certificates were ordered from the vital statistics department of the appropriate state, trust territory, or foreign country. Death certificates or their equivalent were obtained on all appropriate subjects.

All death certificates were coded by two individuals, trained by the National Center for Health Statistics (NCHS) in underlying and multiple cause of death coding procedures, using the International Classification of Diseases, Ninth Edition (1977) coding system. Classification of the underlying cause of death was in accordance with NCHS decision tables. Each coder independently classified the underlying and multiple causes of death and gave the coding worksheet, with each corresponding death certificate, to the coding supervisor, a trained nosologist, for reconciliation. Following reconciliation, one of the coders placed the death code information, by computer terminal, in the death certificate mortality file via a blind verification program designed to mimic the NCHS underlying multiple cause of death coding sheet. At the

conclusion of this initial input of the death codes, a copy of the death certificate was forwarded to NCHS for further validation. The NCHS returned coded death certificates, which were then compared with the Air Force classification. Discordances were resolved in cooperation with NCHS and entered into the data base.

7. Results

Chapter II has reviewed the comprehensive, cohesive, sequential ascertainment process of death in the study populations. This process has resulted in the identification of 50 dead Ranch Hand subjects and 250 dead comparison subjects. Although it is understood that early differential ascertainment occurred in the Ranch Hand members (because of detailed knowledge of the study group), it is judged that the overall comprehensive ascertainment process is currently balanced with respect to the two groups.

Table 3 and Appendix IV contain summary counts by age, job, and race category for all Ranch Handers and their mortality comparisons; these counts reflect mortality as of 31 December 1982, as known on 27 April 1983. In the stratified analyses, the term "at risk" is defined as simply the number of subjects within a specific stratum, and in life table analyses, as the number of subjects entering a specific age bracket. The term "rate" is the proportion of those individuals "at risk" who are dead.

Table 3

OCCUPATIONAL AND RACE SPECIFIC MORTALITY

		Ranch Hand			Comparisons		
Race	Occupation	At Risk	Dead	Rate	At Risk	Dead	Rate
Non-Black	Officer-pilot	349	12	.034	1740	72	.041
	Officer-navigator	80	2	.025	390	13	.033
	Officer-other	25	1	.040	123	3	.024
	Enlisted-flt eng	189	6	.032	935	46	.049
	Enlisted-other	528	25	.047	2628	97	.037
Black	Officer-pilot	6	0	.000	13	0	.000
	Officer-navigator	2	0	.000	10	0	.000
	Officer-other	1	0	.000	2	0	.000
	Enlisted-flt eng	15	2	.133	75	9	.120
	Enlisted-other	52	2	.038	255	10	.039
	TOTAL	1247	50	.040	6171	250	.041

Chapter III

RANCH HAND VERSUS COMPARISON GROUP ANALYSES

1. Introduction

Overall survival comparisons, without regard to cause of death, were made via survival curve estimation, linear rank procedures, relative risk estimation and standardized mortality ratios. Survival curves were estimated and plotted using the method of Kaplan and Meier (6); 95% confidence bands (7) for each survival curve estimate were also plotted on each graph. Linear rank testing was carried out using the logrank test and Prentice's censored data extension of the Wilcoxon test (8). All linear rank tests were carried out with matched sets merged when Ranch Hands differed by less than one year relative to date of birth, within each stratum of job and race (9). These merged matched sets were regarded as separate strata for testing purposes (9, 10, 11). Relative risk estimates and confidence intervals were computed using an extension of the method of Ejigou and McHugh (12) to variable length, one-to-many matched sets (see Appendix V). Here, due to the one-to-many limitation of the algorithm, matched sets were not merged as when testing procedures were performed. Standardized mortality ratios and associated tests and plots were carried out as in Gail (13).

These analyses are fully adjusted for the matching variables, age, race and occupation, but are unadjusted for other variables of interest, such as length of time in Vietnam or Southeast Asia, herbicide dose, time since exposure, time in active duty military, and other medical or occupational risk factors. Some of these variables, such as herbicide dose and time since exposure will be adjusted for in the next analyses, after such data become available. In particular, latency analyses cannot be undertaken at this time but will be included in the next mortality report.

In these analyses, we have used summary statistics for which underlying modeling assumptions can be tested. For this reason, we have used the Breslow-Day (13) approach to SMR calculation, rather than the more traditional person-years method. A detailed explanation of this choice is given in Chapter VI.

2. Overall Comparisons

Survival time in these analyses was regarded as independent of censorship, if any, and was taken to be age at death. All subjects not certifiably dead, as of 31 December 1982, at the time of analysis, were considered censored at their age on that date. Contact has been lost with two Ranch Handers and nine comparisons as described in Chapter II, but these are not assumed lost to follow-up for the purpose of mortality determination. They are assumed to have been alive on 31 December 1982. With this assumption, no subjects were lost to mortality follow-up before 31 December 1982 in this study.

Ranch Hand and comparison group survival curve estimates and their associated 95% confidence bands are shown in Figure 3 and Appendix VI for the five groups: pooled, officers, enlisted, flying and ground personnel, as defined in Table 4. The curves for the pooled groups are shown in Figure 3 with the 95% confidence interval bands deleted in the interest of legibility, but they are included in the group specific curves in Appendix VI. Review of

Ranch Hand operations has strongly suggested that Ranch Hand enlisted personnel were more heavily exposed to herbicide than Ranch Hand officers. Further, there is a perception of possible exposure differential between flying and ground Ranch Hand personnel. These notions prompted the above groupings and analyses seen in this and subsequent chapters. Analyses of latency are not possible at this time due to the as yet incomplete nature of the military service data base. These analyses will be performed after the hand review of military tour records has been completed.

Figure 3

SURVIVAL CURVE ESTIMATES FOR POOLED RANCH HANDERS AND COMPARISON SUBJECTS

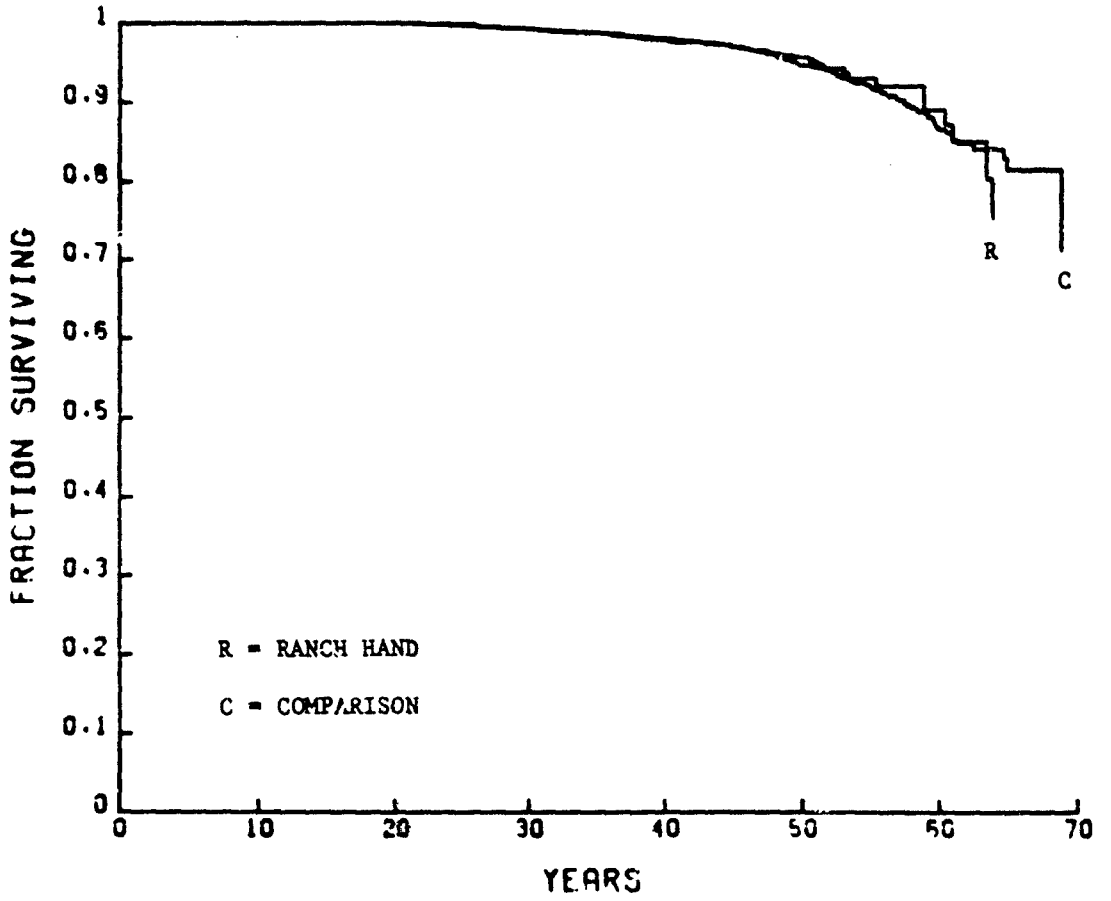


Table 4

GROUP DEFINITIONS

Group	Definition
Officer	Officer-pilot, navigator, other
Enlisted	Enlisted-flight engineer, other
Flying	Officer-pilot, navigator Enlisted-flight engineer
Ground	Officer-other Enlisted-other
Pooled	All occupational categories

Summary counts by group are shown in Table 5. Ignoring the matching, interaction between officer-enlisted categories and Ranch Hand membership, and interaction between flying-ground categories and Ranch Hand membership was evaluated using log-linear models. No statistically significant interactions were detected.

Table 5

SUMMARY COUNTS BY GROUP

	Ranch Hand			Comparisons		
Group	At Risk	Dead	Rate	At Risk	Dead	Rate
Officer	463	15	.032	2278	88	.039
Enlisted	784	35	.045	3893	162	.042
Flying	641	22	.034	3163	140	.044
Ground	606	28	.046	3008	110	.037
Pooled	1247	50	.040	6171	250	.041

Linear rank procedures were carried out on the same five groups. The results, summarized by test statistics and two-sided P-values, are shown in Table 6. Small P-values, less than .05, indicate significant differences, at the 5% level, between the two groups. These procedures are designed so that the statistic will be positive when the Ranch Handers are dying before the comparison subjects and negative when the comparisons are dying prior to the Ranch Handers. The null hypothesis is that the actual survival distributions of Ranch Handers and their matched comparisons are identical. Each statistic is approximately null distributed as a standard normal random deviate.

Table 6

TEST RESULTS AND P-VALUES FOR OVERALL COMPARISONS

Group	Logrank (Value)	Logrank P-Value	Wilcoxon (Value)	Wilcoxon P-Value
Officer	(-0.634)	.526	(-0.722)	.470
Enlisted	(0.383)	.702	(0.331)	.741
Flying	(-1.021)	.307	(-1.116)	.264
Ground	(1.023)	.306	(0.950)	.342
Pooled	(-0.047)	.962	(-0.123)	.902

There is no significant difference, based on these data, between the Ranch Handers and their mortality comparison group. This means that, in particular, the mean ages-at-death of the Ranch Handers and their matched comparisons are not significantly different. In some groups, pooled, officer and flying, the statistics are negative, indicating that the Ranch Handers are living longer than the comparisons, but the differences are, again, insignificant, as evidenced by the large P-values. The situation is reversed for enlisted and ground personnel. These findings are consistent with the observation that, within each group, the comparison confidence bands are contained within the Ranch Hand confidence bands. When matched sets are stratified by five year intervals on year of birth, the same procedures give larger P-values than those in Table 6.

Relative risk estimates, the associated 95% confidence intervals, two-sided P-values for testing the null hypothesis of relative risk equal to unity and the associated power are given in Table 7. Here, the power of the test is defined as the conditional probability of rejecting the null hypothesis at the 5% level of significance, given that the relative risk is equal to its estimated value.

Table 7

RELATIVE RISKS AND 95% CONFIDENCE INTERVALS, P-VALUES AND POWER

Group	Relative Risk	95% Confidence Interval	P-Value	Power
Officer	0.763	(.320 - 1.207)	.373	.105
Enlisted	1.065	(.660 - 1.471)	.742	.072
Flying	0.734	(.387 - 1.081)	.211	.197
Ground	1.232	(.694 - 1.769)	.337	.195
Pooled	0.964	(.658 - 1.269)	.819	.051

The confidence intervals and P-values in Table 7 indicate no significant difference, at the 5% level, between the mortality of the Ranch Handers and comparisons in each of the five groups.

Year-of-birth specific mortality rates for each of the five groups are given in Tables 8 through 12, with the corresponding standardized mortality ratios (SMR). In each group, the comparisons are the internal standard. The SMR estimates relative risk in these comparisons if the year-of-birth specific relative risks are all equal (13). A likelihood ratio test for the hypothesis of equal year-of-birth specific relative risks was carried out for each comparison; its P-value is denoted by P1. In addition, the hypothesis that relative risk is unity, given that relative risk is constant across strata, was tested via a likelihood ratio procedure (13); its P-value is denoted by P2. The SMR and both P-values are given with each comparison.

Here, and elsewhere in this report, the denominator of the SMR is $\sum n_{ij} r_i$, where n_{ij} is the number of individuals for the ith stratum of the jth population and r_i is the death rate, per person, in the standard population for the ith stratum. In these calculations the data is stratified on year of birth.

Table 8

POOLED SPECIFIC MORTALITY RATES BY YEAR OF BIRTH
(SMR = .996; P1=.389, P2=.955)

Birth Year	Ranch Handers			Comparison		
	At Risk	Dead	Rate	At Risk	Dead	Rate
1905-14	5	2	.400	14	2	.143
1915-19	17	4	.235	96	11	.115
1920-24	48	3	.063	241	24	.100
1925-29	84	2	.024	501	40	.080
1930-34	304	15	.049	1389	67	.048
1935-39	207	7	.034	1020	33	.032
1940-44	208	5	.024	1096	23	.021
1945-54	374	12	.032	1814	50	.028
		50			250	

Table 9

OFFICER SPECIFIC MORTALITY RATES BY YEAR OF BIRTH
(SMR = .827; P1=.233, P2=.490)

Birth Year	Ranch Hand Officers			Comparison Officers		
	At Risk	Dead	Rate	At Risk	Dead	Rate
1910-24	41	3	.073	205	17	.083
1925-34	194	4	.021	930	49	.053
1935-39	93	4	.043	458	11	.024
1940-44	90	2	.022	495	6	.012
1945-49	45	2	.044	190	5	.026
		15			88	

Table 10

ENLISTED SPECIFIC MORTALITY RATES BY YEAR OF BIRTH
(SMR = 1.074; P1=.733, P2=.722)

Birth Year	Enlisted Ranch Handers			Enlisted Comparisons		
	At Risk	Dead	Rate	At Risk	Dead	Rate
1905-14	4	2	.500	12	2	.167
1915-19	9	1	.111	54	7	.130
1920-24	16	3	.188	80	11	.138
1925-29	41	2	.049	211	22	.104
1930-34	153	11	.072	749	36	.048
1935-39	114	3	.026	562	22	.039
1940-44	118	3	.025	601	17	.028
1945-54	329	10	.030	1624	45	.028
		35			162	

Table 11

FLYING SPECIFIC MORTALITY RATES BY YEAR OF BIRTH
(SMR = .769; P1=.678, P2=.238)

Birth Year	Flying Ranch Handers			Flying Comparisons		
	At Risk	Dead	Rate	At Risk	Dead	Rate
1915-24	44	4	.091	220	23	.105
1925-34	272	8	.029	1316	71	.054
1935-39	142	6	.042	698	22	.032
1940-44	120	2	.017	653	14	.021
1945-49	63	2	.032	276	10	.036
		22			140	

Table 12

GROUND SPECIFIC MORTALITY RATES BY YEAR OF BIRTH
(SMR = 1.257; P1=.535, P2=.302)

Birth Year	Ground Ranch Handers			Ground Comparisons		
	At Risk	Dead	Rate	At Risk	Dead	Rate
1905-14	5	2	.400	14	2	.143
1915-24	21	3	.143	117	12	.103
1925-29	31	2	.065	151	19	.126
1930-34	85	7	.082	423	17	.040
1935-39	65	1	.015	322	11	.034
1940-44	88	3	.034	443	9	.020
1945-54	311	10	.032	1538	40	.026
		28			110	

These SMR comparisons are in agreement with the preceding relative risk and linear rank analyses; there is no significant difference in mortality, based on these data, between the Ranch Hand group and the comparison group.

3. Noncause Specific Occupational Comparisons

Within-group comparisons by occupation via SMR's, with P-values for testing constant relative risk across year of birth strata (P1) and for testing relative risk equal to unity (P2) are given in Tables 13 through 16. The enlisted and ground personnel are the internal standards in these comparisons. Comparisons via the logrank procedure are given in Table 17.

Table 13

RANCH HAND OFFICERS VERSUS RANCH HAND ENLISTED
MORTALITY BY YEAR OF BIRTH
(SMR = .544; P1=.280, P2= .087)

Birth Year	Ranch Hand Officers			Ranch Hand Enlisted		
	At risk	Dead	Rate	At Risk	Dead	Rate
1905-24	41	3	.073	29	6	.207
1925-34	194	4	.021	194	13	.067
1935-39	93	4	.043	114	3	.026
1940-44	90	2	.022	118	3	.025
1945-54	45	2	.044	329	10	.030
		15			35	

Table 14

RANCH HAND FLYING PERSONNEL VERSUS RANCH HAND GROUND PERSONNEL
MORTALITY BY YEAR OF BIRTH
(SMR = .581; P1=.382, P2=.100)

Birth Year	Ranch Hand Fliers			Ranch Hand Ground		
	At Risk	Dead	Rate	At Risk	Dead	Rate
1905-24	44	4	.091	26	5	.192
1925-34	272	8	.029	116	9	.078
1935-39	142	6	.042	65	1	.015
1940-44	120	2	.017	88	3	.034
1945-54	63	2	.032	311	10	.032
		22			28	

Table 15

COMPARISON GROUP OFFICERS VERSUS COMPARISON GROUP ENLISTED
MORTALITY BY YEAR OF BIRTH
(SMR = .697; P1=.640, P2=.015)

Birth Year	Comparison Officers			Comparison Enlisted		
	At Risk	Dead	Rate	At Risk	Dead	Rate
1905-19	44	4	.091	66	9	.136
1920-24	151	13	.081	80	11	.138
1925-29	290	18	.062	211	22	.104
1930-34	640	31	.048	749	36	.048
1935-39	458	11	.024	562	22	.039
1940-44	495	6	.012	601	17	.028
1945-54	190	5	.026	1624	45	.028
		88			162	

Table 16

COMPARISON FLYING PERSONNEL VERSUS COMPARISON GROUND
MORTALITY BY YEAR OF BIRTH
(SMR = .930; P1=.305, P2=.867)

Birth Year	Comparison Fliers			Comparison Ground		
	At Risk	Dead	Rate	At Risk	Dead	Rate
1905-19	45	6	.133	65	7	.108
1920-24	175	17	.097	66	7	.106
1925-29	350	21	.060	151	19	.126
1930-34	966	50	.052	423	17	.040
1935-39	698	22	.032	322	11	.034
1940-44	653	14	.021	443	9	.020
1945-54	276	10	.036	1538	40	.026
		140			110	

Table 17

LOGRANK WITHIN GROUP COMPARISONS

Comparison	Logrank	P-Value
RH Officer vs RH Enlisted	-1.468	0.142
RH Flyers vs RH Ground	-1.455	0.146
Comparison Officer vs Comp Enlisted	-2.597	0.009
Comparison Flyers vs Comp Ground	-0.363	0.717

The SMR and logrank analyses are somewhat in agreement, with both procedures finding significant differences between comparison officers and comparison enlisted, with the officers living longer. The two methods approximately agree on the Ranch Hand fliers versus ground personnel and on Ranch Hand officer versus enlisted personnel with the logrank result near significance at the .10 level; the fliers appear to be living longer than the ground personnel within the Ranch Hand group.

4. Cause Specific Ranch Hand Versus Comparison Mortality

Cause specific mortality, relative risks, two-sided P-values for testing relative risk equal to unity, power and 95% confidence intervals for relative risks are summarized in Table 18 for the 1241 matched Ranch Handers and their mortality comparisons. Mortality data for the six unmatched Ranch Handers were not used in this analysis. Of the six, one has died of an accident and the rest are still alive. In some categories, the data were too sparse for relative risk estimation.

Table 18

CAUSE SPECIFIC MORTALITY AND RELATIVE RISKS

Cause	Dead RH	Dead Comparison	Relative Risk	95% Conf Int.	P-value	Power
Accidental	18	92	.959	(.466 - 1.453)	.875	.047
Suicide	3	14	1.071	(0 - 2.407)	.913	.061
Homicide	2	3	3.333	(0 - 9.297)	.099	.489
Infectious, Parasitic	0	3				
Malignant Neoplasm	4	39	.503	(0 - 1.024)	.205	.153
Uncertain Neoplasm	0	2				
Endocrine	1	1	5.000	(0 -18.859)	.102	.562
Mental Disorder	0	1				
Nervous System	0	2				
Circulatory	16	70	1.002	(.411 - 1.594)	.994	.050
Respiratory	0	4				
Digestive	5	11	2.273	(0 - 4.675)	.085	.457
Genitourinary	0	3				
Ill Defined	0	2				
Unknown	0	3				
	49	250				

The low powers in Table 18 reflect the sparseness of data or the fact that some of the observed relative risks approach unity. However, two categories do stand out as deserving further attention: malignant neoplasms and digestive system deaths. It should be noted that if matched sets are ignored and relative risk is estimated using the method of Mantel and Haenszel (14), these results remain essentially unchanged; using this approach, the relative risk for malignant neoplasms, for example, is .506 with a P-value of .195 and power equal to .254. The 95% confidence interval for relative risk using this approach is .180 to 1.419. The Mantel-Haenszel relative risk for the digestive system comparison is 2.254, with a P-value of .132 and a power equal to .325; the 95% confidence interval for relative risk is .782 to 6.501. The digestive system deaths are further defined in Table 19. There has been an increase in deaths due to liver disease among the Ranch Handers; however, this observed difference is not statistically significant. These data are also based on death certificate diagnoses and will be subjected to verification and validation from medical record and autopsy reports. When all deaths from liver disease are considered as a whole, a relative risk of 2.50 is found, with a 95% confidence interval of 0 to 5.501. The P value is 0.083. Similarly, the relative risk for pancreatitis is 2.50 with a 95% confidence interval of 0 to 8.501.; the P value is 0.386. These observations are of interest and will be pursued in depth in subsequent reports.

Table 19

DIGESTIVE SYSTEM MORTALITY

ICD Code (9th Ed)	Deaths	
	Ranch Hand	Comparison
Pancreatitis (5770)	1	2
Alcoholic cirrhosis (5712)	0	3
Nonalcoholic cirrhosis (5715)	3	3
Nonalcoholic fatty liver (5718)	0	1
Chronic liver disease (5728)	0	1
Alcoholic liver disease (5711)	1	0
Duodenal ulcer (5325)	0	1
	5	11

Table 20

SITE SPECIFIC MALIGNANT NEOPLASM MORTALITY

Site ICD Code (9th Ed)	Deaths	
	Ranch Hand	Comparison
Lip, oral cavity, Pharynx (140-149)	0	4
Digestive organs, peritoneum (150-159)	0	8
Respiratory, intrathoracic (160-165)	2	15
Bone, connective tissue, skin, breast (170-175)	0	1
Genitourinary organs (179-189)	1	3
Brain (191-192)	0	3
Lymphatic and hematopoietic tissue (200-208)	0	4
No site specification (199)	1	1
	4	39

The malignant neoplasms are detailed in Table 20, the cell types of the neoplasms, as recorded on the death certificates, are summarized in Table 21.

Table 21

MORPHOLOGY OF NEOPLASMS

ICD Code 9th Ed.	Nomenclature	Deaths Ranch Hand	Deaths Comparison
M800	Neoplasms not otherwise specified (NOS)		
	Brain	0	1
	Bronchus and Lung	0	3
	Colon	0	1
	Intestinal Tract	0	1
M801-804	Epithelial neoplasms (NOS)		
	Bronchus and Lung	1	8
	Esophagus	0	1
	Kidney	1	1
	Nasopharynx	0	1
	Pancreas	0	2
	Unspecified site	1	1
M805-808	Papillary and Squamous Cell		
	Nasal Sinus	0	1
	Lip	0	1
	Tongue	0	1
	Tonsil	0	1
M814-838	Andenomas and Adenocarcinomas		
	Appendix	0	1
	Bronchus and Lung	0	2
	Colon	0	1
	Kidney	0	2
	Stomach	0	1
M872-879	Nevi and Melanomas		
	Skin (NOS)	0	1
	Mediastinal	1	0
M905	Mesothelioma		
	Bronchus and Lung	0	1
M938-948	Gliomas		
	Frontal Lobe	0	1
	Brain (NOS)	0	1
M959-963	Lymphomas NOS and Diffuse		
	Lymphomas (NOS)	0	1
M965-966	Hodgkins disease		
	Hodgkin's (NOS)	0	2
M986	Myeloid Leukemias		
	Acute Myelocytic Leukemia	0	1
		4	39

Epithelial, papillary and adenomas account for 64% of the comparison neoplasms. Three Ranch Hand neoplasms arose from epithelial cells. There were no tumors in either group which were classified as soft tissue sarcoma.

Chapter IV

NONCAUSE SPECIFIC COMPARISONS WITH EXTERNAL POPULATIONS

1. Background and Motivation

It is important to know, not only how the Ranch Handers and their matched comparisons relate to each other, but also how they compare with general military and male United States populations. Pitfalls inherent in these comparisons are well known and are briefly reviewed below for specific comparisons with 1978 DoD period life tables for nondisability retired military officer and enlisted personnel (15) and the 1978 U.S. White Male Life Table (16). Although there are difficulties in the use of these comparisons, their use does provide an additional indicator of trends in mortality when viewed in the context of the total analytic process.

2. Adjustment Difficulties

Mortality rates in any military population are strongly dependent upon 1) calendar year of death, 2) military status (active duty, separated, retired), 3) selection and retention, and 4) branch of service. Adjustment for these effects was not made in these comparisons because published select Air Force life tables, by calendar year and by status, are not available. In addition, there is also a problem with the statistical method used, since the Gail and Ware (17) procedure assumes constant relative risk with respect to age; the selection effect has been shown to diminish sharply with time making this assumption untenable in these comparisons. The adjustment difficulties (1-4), and their likely consequences, are detailed below. These difficulties apply to all of the comparison groups, but these concerns have less effect on the comparisons of the Ranch Hand group to their matched cohort since these two groups are generally equivalent, relative to these key factors.

A. Adjustment for Calendar Year of Death

Due to the continuing decrease in overall mortality in the military (18) and in the United States (19), the referenced external age-specific rates are appropriate only for the calendar period of the referenced external life table, that is, 1977-79 for the 1978 period military table used in this analysis. The 1977-79 period rates would, for example, be too low for comparison with subjects dying in 1970 at the age of 40. These subjects would more properly be compared with the death rate for 40 year olds in a 1970 period life table or with a death rate for 40 year olds in a cohort military life table for subjects born in 1930. Calendar time is not taken into account in this analysis because period life tables covering the three decades from 1950 to 1980, for the the active duty, separated and retired Air Force subpopulations, are not currently available. This discrepancy is serious because the decline in death rates in the active duty Air Force during the period 1966 to 1980 has been very substantial (18).

B. Adjustment for Military Status (Active Duty, Separated, Retired).

The only published military life tables available at this writing are 1978 period tables for DoD nondisability retired officer and enlisted personnel (15) and a series of yearly abridged tables for the active duty Air Force, the first covering the period 1966-1968 and the last, 1978-1980 (18). With these data limitations, adjustment for military status is not possible. It is

clear, however, that there are substantial differences between active duty and retired death rates with the active duty rates being lower than retired rates (15).

C. Adjustment for Selection

Entry into the military carries with it an effect known as selection, a lengthening of life expectancy due to health prerequisites upon entry into select status and periodic health checks thereafter. This effect is well known to insurance actuaries who have observed that, in insured populations, the effect diminishes as time passes unless there are continued checks on the state of health of the insured persons (20). If selection is to be adjusted for in this analysis, it would be necessary to know Air Force death rates as a function of both age and of time elapsed since entry into the Air Force. It would also be necessary, therefore, to know enlistment and discharge or retirement dates for all study subjects. It is the lack of these data that makes this adjustment impossible at this time. The consequences of this lack of adjustment are not known at this writing.

D. Adjustment for Branch of Service

Age specific active duty Air Force death rates are substantially lower than the corresponding rates for other services (18). Nonservice specific death rates are therefore too high for appropriate comparison with these two study groups.

3. Comparisons with 1978 DoD Life Tables

In Tables 22 and 23, Ranch Hand officers and comparison group officers are contrasted to a 1978 DoD nondisability retired officer life table (15) and in Tables 24 and 25, Ranch Hand and comparison group enlisted personnel are compared with a 1978 DoD nondisability retired enlisted life table (15). In each table, the column labeled "At Risk" lists the number of subjects entering each five year age interval, the column labeled "Deaths" tabulates the numbers of deaths in the age intervals and the column labeled "Expected Deaths" gives the expected numbers of deaths in the age intervals if the study subjects had experienced the same death rates as those specified by the DoD table. The value of the test statistic (17) for testing the null hypothesis of equality is denoted by T; its two-sided P-value is denoted by P. While each table summarizes the findings with five year age intervals for ease of presentation, one year age intervals were used for the computation of the statistic T. All comparisons are conditioned on survival to age 35, since the DoD tables begin at that age. All comparisons are unadjusted for race since the DoD tables are not race specific.

Table 22

RANCH HAND OFFICER VERSUS DOD NONDISABILITY
RETIRED OFFICER LIFE TABLE
(T = -3.962, P < .001)

Age	At Risk	Deaths	Expected Deaths
35-39	456	2	4.183
40-44	366	1	4.244
45-49	288	1	4.578
50-54	173	1	3.099
55-59	57	1	2.043
60-64	30	2	.823
65-68	1	0	.076
		8	19.046

Table 23

COMPARISON OFFICERS VERSUS DOD NONDISABILITY
RETIRED OFFICER LIFE TABLE
(T = -2.402, P = .016)

Age	At Risk	Deaths	Expected Deaths
35-39	2264	12	20.837
40-44	1822	13	20.703
45-49	1365	24	21.920
50-54	842	12	15.901
55-59	308	9	10.265
60-64	145	4	4.377
65-68	19	0	.601
		74	94.604

Table 24

ENLISTED RANCH HANDERS VERSUS DOD NONDISABILITY
RETIRED ENLISTED LIFE TABLE
(T = -.239, P = .811)

Age	At Risk	Deaths	Expected Deaths
35-39	668	6	6.748
40-44	392	5	5.601
45-49	287	5	6.326
50-54	140	5	4.154
55-59	41	2	2.203
60-64	20	2	1.484
65-69	6	0	.576
70-71	1	1	.096
		26	27.188

ENLISTED COMPARISON SUBJECTS VERSUS DOD NONDISABILITY
RETIRED ENLISTED LIFE TABLE
(T = -3.214, P = .001)

Age	At Risk	Deaths	Expected Deaths
35-39	3299	21	33.370
40-44	1945	20	27.681
45-49	1437	31	31.450
50-54	695	14	20.076
55-59	203	12	10.980
60-64	103	3	7.515
65-59	35	1	2.593
70-74	5	0	.646
		102	134.311

These findings suggest that, if the effects discussed in section 2 are assumed to be negligible, Ranch Hand officers and comparison officers and comparison enlisted personnel are living longer than expected relative to their respective external populations. Enlisted Ranch Hand personnel are not different from DoD enlisted personnel. In the above DoD comparison there is a suggestion of interaction between officer-enlisted categories and Ranch Hand versus comparison group membership. If matching and time of death are ignored, the following table can be constructed. The term "rate" is as defined on page 8 of this report.

Table 26

DEATH AFTER 35 YEARS

	Ranch Hand			Comparison		
	Alive	Dead	Rate	Alive	Dead	Rate
Officer	448	8	.018	2190	74	.033
Enlisted	642	26	.039	3197	102	.031

Analysis using log-linear models shows a statistically significant interaction with $p \leq 0.05$. It appears that Ranch Hand officers have a lower mortality after age 35 than Ranch Hand enlisted or comparison officers or enlisted. However, the converse situation is noted considering mortality prior to age 35 and is significant with $p \leq 0.05$. The data for this analysis of mortality prior to age 35 is set out below.

Table 27

DEATHS BEFORE AGE 35 YEAR

	Ranch Hand			Comparison		
	Alive	Dead	Rate	Alive	Dead	Rate
Officer	456	7	.015	2264	14	.006
Enlisted	775	9	.011	3833	60	.015

These interactions will require further detailed analysis and evaluation, with specific consideration of medical covariables including risk taking, other life patterns and herbicide.

4. Comparisons with U.S. 1978 White Male Life Table

Non-Black Ranch Handers and non-Black comparisons are compared in this section with the population of White males, as represented by the 1978 U.S. White Male Life Table (16). Two serious and well known problems with the use of this table are the lack of adjustments for the calendar year and selection effects just described; when comparing occupational cohorts with national populations, the selection effect is known as the "healthy worker" effect. The pitfalls of these kinds of comparisons are well documented (21, 22, 23). In Tables 28 and 29, non-Black Ranch Handers and non-Black comparisons are compared, via the method of Gail and Ware (17), with the 1978 U.S. White Male Life Table (16). In Tables 30 through 33, non-Black officers and enlisted personnel in both study groups are compared with the same 1978 U.S. White Male Table.

Table 28

NON-BLACK RANCH HANDERS VERSUS 1978 U.S. WHITE MALE LIFE TABLE
(T=-4.588, P <.001)

Age	At Risk	Deaths	Expected Deaths
21-24	1171	2	9.003
25-29	1169	6	9.783
30-34	1163	7	9.396
35-39	1054	7	9.256
40-44	722	5	10.381
45-49	549	6	12.085
50-54	304	5	8.114
55-59	98	3	5.039
60-64	50	4	2.790
65-69	7	0	0.669
70-71	1	1	0.089
		46	76.605

Table 29

NON-BLACK COMPARISONS VERSUS THE 1978 U.S. WHITE MALE LIFE TABLE
(T = -11.230, P <.001)

Age	At Risk	Deaths	Expected Death
19-19	5816	1	10.325
20-24	5815	16	55.444
25-29	5799	27	48.592
30-34	5772	23	46.719
35-39	5245	31	46.124
40-44	3593	29	51.041
45-49	2675	50	58.810
50-54	1487	26	40.529
55-59	509	20	25.210
60-64	248	7	14.461
65-69	54	1	3.403
70-74	5	0	0.601
		231	354.540

Table 30

NON-BLACK RANCH HAND OFFICERS VERSUS 1978 U.S. WHITE MALE LIFE TABLE
(T = -4.575, P < .001)

Age	At Risk	Deaths	Expected Deaths
25-29	454	3	3.794
30-34	451	4	3.710
35-39	447	2	4.420
40-44	362	1	5.304
45-49	285	1	6.370
50-54	172	1	4.541
55-59	57	1	3.019
60-64	30	2	1.302
65-68	1	0	0.110
		15	32.570

Table 31

NON-BLACK COMPARISON OFFICERS VERSUS 1978 U.S. WHITE MALE
LIFE TABLE
(T = -7.923, P < .001)

Age	At Risk	Deaths	Expected Deaths
25-29	2253	9	18.880
30-34	2244	5	18.530
35-39	2239	12	22.137
40-44	1801	13	25.841
45-49	1352	24	30.468
50-54	834	12	23.328
55-59	308	9	15.157
60-64	145	4	6.923
65-68	19	0	0.887
		88	162.151

Table 32

NON-BLACK RANCH HAND ENLISTED PERSONNEL VERSUS 1978 U.S. WHITE MALE
LIFE TABLE
(T = -1.753, P = .080)

Age	At Risk	Deaths	Expected Deaths
21-24	717	2	5.510
25-29	715	3	5.988
30-34	712	3	5.686
35-39	607	5	4.836
40-44	360	4	5.077
45-49	264	5	5.716
50-54	132	4	3.573
55-59	41	2	2.020
60-64	20	2	1.488
65-69	6	0	0.588
70-71	1	1	0.089
		33	40.571

Table 33

NON-BLACK COMPARISON ENLISTED PERSONNEL VERSUS THE 1978 U.S. WHITE MALE LIFE TABLE
(T =-5.923, P < .001)

Age	At Risk	Deaths	Expected Death
19-19	3563	1	6.325
20-24	3562	16	33.938
25-29	3546	18	29.713
30-34	3528	18	28.189
35-39	3006	19	23.987
40-44	1792	16	25.200
45-49	1323	26	28.341
50-54	653	14	17.201
55-59	201	11	10.053
60-64	103	3	7.538
65-69	35	1	2.515
70-74	5	0	0.601
		143	213.601

Given the cautions just described, these findings suggest that the non-Black Ranch Handers and comparisons are living much longer than expected relative to the 1978 U.S. White Male Life Table. The ratios of the observed to the expected deaths described in Tables 28 and 29 reveal that the Ranch Hand and comparison subjects are experiencing death at only 60 to 65% of the rate of the U.S. White male population. The ratio is 0.461 for the subset of Ranch Hand officers, 0.543 for comparison officers, 0.813 for enlisted Ranch Handers, and 0.669 for enlisted comparison subjects. The healthy worker effect is very likely a major contributor to the undoubtedly real differences between these study groups and the general population.

Chapter V

COMPARISONS WITH THE WEST POINT STUDY GROUP

1. Background and Motivation

The statistical and epidemiological literature is replete with warnings against the uncritical use of the SMR and related summary measures for comparing study groups with published vital statistics for national populations or subpopulations (5), (24), (25). Those cautions are based on the adjustment difficulties described in Chapter 4, Section 2, and departures from the assumption of constant relative risk across age intervals between the study group and the external population. These drawbacks can be avoided by not referencing an external standard at all, by using one of the study groups as the standard (13), or by using as an external standard a group of military personnel, born during approximately the same years, with the same mortality follow-up, as the Ranch Hand and comparison groups.

An external group of sufficient size for meaningful statistical comparisons is not available at this time. Mortality and year of birth data are available, however, on a small group of West Point graduates, the subjects of the West Point Follow-up Study. Although this group is too small for all but very crude statistical comparisons (1), it is the only known external data available at this time. The following comparisons are, therefore, primarily descriptive.

The West Point Study Group consists of 474 members of the West Point graduation class of 1956. These men have been followed up since then for morbidity and mortality. All members of that class were, or still are, officers in the U.S. Armed Forces. The purpose of the West Point study is to investigate the relationship between blood lipid levels and cardiovascular disease. Each study subject is physically examined biennially and blood samples are obtained for lipid and lipoprotein analyses at the USAF School of Aerospace Medicine (26).

2. Noncause Specific Comparisons of Ranch Hand and Comparison Subgroups with the West Point Study Group

For the purpose of these mortality comparisons, 15 of the 36 known West Point deaths occurring on or before 31 December 1982 were deleted, 9 of the 15 were killed in action, one was killed in 1959 in the line of duty and 5 were killed in automobile crashes prior to 1962. These deletions imitate the deletion of personnel killed in action from the Ranch Hand and comparison groups. Noncombat or accidental deaths prior to 1962 were deleted because death prior to 1962 would have precluded membership in the Ranch Hand or comparison groups. In addition, one West Pointer who is also a Ranch Hander, was deleted; that individual was alive on 31 December 1982.

A summary of the remaining 21 deaths among the 458 West Point subjects used in these analyses is given by year of birth in Table 34 and by age in Table 35. In Table 35 the column headed "censored" lists by age, the number of West Pointers alive on 31 December 1982.

Table 34

WEST POINT DEATHS BY YEAR OF BIRTH

Year of Birth	At Risk	Dead
1930	20	0
1931	59	2
1932	90	6
1933	136	8
1934	141	4
1935	12	1
	458	21

Table 35

WEST POINT DEATHS BY AGE

Age	At Risk	Censored	Dead
25-29	458	0	2
30-34	456	0	5
35-39	451	0	3
40-44	448	0	2
45-49	446	276	8
50-52	162	161	1
		437	21

In this analysis, non-Black Ranch Hand and comparison officers are compared, without regard to cause of death, with the West Point study group; all of the West Point subjects are non-Black. Non-Black Ranch Hand Officers were matched, one-to-one, by year of birth, to West Point subjects. Due to the relatively small number of Ranch Hand officers and the limited year of birth range imposed by the age of the Class of 1956, only 283 of the 458 West Point subjects received a matched Ranch Hander. Matched sets with West Pointers having the same year of birth were then merged to create six matched sets, corresponding to the six years of birth, 1930 through 35, of the West Pointers. To compare West Pointers with comparison officers, two non-Black comparison officers were matched to each West Pointer by year of birth. All West Pointers received two matched comparison individuals. Matched sets with West Pointers having the same year of birth were merged, giving six matched sets containing a total of 916 comparisons.

Logrank tests were carried out on these two matched data sets, and the results are summarized in Table 36. In these analyses, survival time is age at death. Censorship is due to survival to 31 December 1982. For those still alive on 31 December 1982, censoring time is age on that day.

Table 36

STUDY GROUP VERSUS WEST POINT GROUP
LOGRANK COMPARISONS WITH TWO-SIDED P-VALUES

Comparison	P-Value
Ranch Hand officer versus West Point	.218
Comparison officer versus West Point	.528

An SMR analysis, with the West Pointers being the standard, is summarized in Table 37.

Table 37

SMR COMPARISON OF NON-BLACK RANCH HAND AND COMPARISON OFFICERS WITH THE WEST POINT STUDY GROUP

	(SMR = .530)			(SMR = .778)			(SMR = 1)		
Birth	Ranch Hand			Comparison			West Point		
Year	At Risk	Dead	Rate	At Risk	Dead	Rate	At Risk	Dead	Rate
25-31	95	2	.021	272	19	.070	79	2	.025
32	35	1	.029	164	7	.043	90	6	.067
33-34	60	1	.017	257	6	.023	277	12	.043
35-40	93	4	.043	223	5	.022	12	1	.083
		8			37			21	

The test for constant relative risk across year of birth strata gives a P-value of .229. Further, a likelihood ratio test suggests that these SMR's are not different (P = .392).

3. Cause Specific Comparisons

The cause specific death counts for the West Point Study Group are given in Table 38.

Table 38
WEST POINT MORTALITY BY CAUSE

Cause	Count
Accidents	6
Infectious disease	1
Malignant neoplasms	6
Circulatory	5
Digestive	1
Genitourinary	1
Ill defined	1
	21

Cause specific comparisons are carried out with three causes, cancer (malignant neoplasms), other diseases, and nondisease (accidents, suicides, homicides and ill-defined), with an adjustment for year of birth by stratification on year of birth. Relative risks are calculated using the method of Mantel and Haenszel (14). These results, based on the counts in Tables 39 and 40, are shown in Table 41.

Table 39

CAUSE SPECIFIC COMPARISONS
RANCH HAND OFFICERS VERSUS WEST POINT

		Ranch Hand		West Point	
Cause	Birth Year	At Risk	Dead	At Risk	Dead
Nondisease	1925-1933	166	1	305	5
	1934-1940	117	4	153	1
Cancer	1925-1930	72	0	20	0
	1931	23	0	59	1
	1932	35	0	90	3
	1933	36	0	136	1
	1934	24	0	141	1
	1935-1940	93	0	12	0
Other diseases	1925-1934	190	2	446	8
	1935-1940	93	1	12	1

Table 40

CAUSE SPECIFIC COMPARISON
COMPARISON OFFICERS VERSUS WEST POINT

Cause	Birth Year	Comparisons		West Point	
		Number	Dead	Number	Dead
Nondisease	1929-1931	272	11	79	1
	1932	164	2	90	2
	1933	148	1	136	2
	1934-1937	332	2	153	1
Cancer	1929-1931	272	2	79	1
	1932	164	2	90	3
	1933	148	1	136	1
	1934-1937	332	2	153	1
Other diseases	1929-1932	436	9	169	1
	1933	148	1	136	5
	1934	109	1	141	2
	1935-1937	223	3	12	1

Table 41

CAUSE SPECIFIC RELATIVE RISKS, P-VALUES
95% CONFIDENCE INTERVALS FOR LOG RELATIVE RISK

Cause	Comparison	RR	95% Conf Interval for Log Rel Risk	P-value	Power
Nondisease	RH vs WP	1.072	(-1.504 - 1.643)	.931	.051
	Comp vs WP	0.841	(-1.354 - 1.009)	.775	.059
Cancer	RH vs WP				
	Comp vs WP	0.690	(-1.634 - .891)	.564	.089
Other diseases	RH vs WP	0.474	(-3.540 - 2.047)	.600	.082
	Comp vs WP	0.779	(-2.367 - 1.867)	.817	.056
All causes	RH vs WP	0.539	(-2.191 - .954)	.441	.120
	Comp vs WP	0.728	(-1.940 - .306)	.702	.067

While the Ranch Hand versus West Point cancer comparison cannot be assessed using the Mantel-Haenszel procedure, the absence of Ranch Hand cancer deaths in this analysis is of interest. This finding is consistent with the apparent but nonsignificantly decreased Ranch Hand cancer mortality noted in the Ranch Hand versus matched comparison group analysis (Chapter III).

Chapter VI

STATISTICAL ASPECTS

1. Purpose

The purposes of this chapter are 1) to briefly describe each statistical procedure used in the preceding chapters 2) to state the underlying assumptions of each procedure and 3) discuss the validity of those assumptions in this study. The procedures used in this analysis were survival curve estimates and confidence bands, linear rank tests, relative risk estimation and standardized mortality ratios. Points 1-3 are addressed for each procedure in Sections 2 through 5.

2. Survival Curve Estimation and Confidence Bands

The survival function of a homogeneous population, S(t), is defined as the probability of surviving t years. The problem is to estimate S(t) and make a confidence statement about that estimate based on randomly censored data Randomly censored data occur in survival studies since analyses are usually carried out before all subjects have failed. In the present application, failure is defined as death and censorship occurs because most subjects are still living at the time of analysis. Other causes for censorship in this kind of epidemiological study are loss to follow-up or death from causes other than those of interest. Thus far in this study, there have been no subjects lost to follow-up, and all causes of death are of interest.

The survival function is estimated here by the product limit estimate K(t), also called the Kaplan-Meier estimate (6). This estimate is derived under the assumption that, in a life testing experiment with n subjects on test, exactly k subjects, with k less than n, are observed to fail; the other n-k remaining are observed only until they are censored. The subjects are assumed drawn randomly from a homogeneous population. Censorship is assumed to be independent of failure. The Kaplan-Meier estimator is asymptotically unbiased and reduces to one minus the empirical distribution function in the absence of censoring.

In the present application, the homogeneous populations are the Ranch Handers, the comparisons and various subgroups of these two groups. Death time is taken as age at death measured to the nearest month; censoring time is age on 31 December 1982, measured to the nearest month. Survival time is age at death or age on 31 December 1982 for those subjects still living.

The process $n[K(t)-S(t)]$ converges weakly to a zero mean Gaussian process, as n tends to infinity, under random censorship when the underlying survival function S(t) and the censoring distribution are continuous on a bounded interval (27). This convergence is the theoretical basis for the confidence band algorithm (7) used in Figures 2 and 3, Chapter III and Appendices VI.

The independence of death and censorship can be assumed to hold here since censorship (survival to December 31, 1982) is not being invoked on individuals because they appear to be at unusually high, or low, risk of death (28). Direct contact has been lost with two Ranch Handers and nine comparisons as described in Chapter II, but these are assumed to be alive, and hence censored at their age on 31 December 1982. The reason for this assumption is that the extensive death ascertainment system is believed to be thorough enough so that, had any of these subjects died, the death would have been detected. Hence, while contact has been lost, loss to follow-up for the purpose of mortality determination has not occurred (29). All other subjects still alive on 31 December 1982 are censored at their age on that date.

The validity of inferences based on the estimate K(t) and its associated confidence band depends on the sample size and the observed number of deaths. The sample sizes and numbers of deaths in every stratum used in these analyses exceed the minimum requirements for these procedures (7).

The survival curve estimates and confidence bands displayed in Figures 2 and 3 and Appendix VI are not adjusted for year of birth. To do so would have required stratification on year of birth, creating many small strata with associated sample size difficulties. Some year-of-birth adjusted plots in the larger occupational strata will be presented in the next report.

3. Linear Rank Procedures

The hypothesis of interest in this analysis is that the actual survival distributions of the Ranch Handers and their matched comparisons are identical. The procedures of choice for testing equality of the two unknown survival distributions based on the matched and censored data in this study are the censored data extensions of the exponential scores and Wilcoxon tests, due to Prentice (8). The first of these is widely known as the logrank test. The test statistics, T, are of the form given by equation 6-23 of (28), where the summands are calculated on matched sets consisting of survival information on one Ranch Hander and his matched mortality comparisons. The statistic T, for either logrank or generalized Wilcoxon summands, is approximately standard normal under the null hypothesis (9).

The large sample normal approximation for T will hold when all distributions are continuous and all censoring times are mutually independent of each other and independent of death. These assumptions are well satisfied in this study since the censorship mechanism, survival to time of analysis, does not favor one group over the other.

In these procedures, the sampling unit is a matched set, so that these tests are adjusted for all matching variables. Prior to calculation, matched sets with Ranch Handers in the same race and job classification having the same year of birth are merged.

The logrank and extended Wilcoxon tests are locally most powerful when the logarithm of the survival times are distributed as extreme value or logistic random variates, respectively. While the efficiency of these procedures peaks at these two underlying distributions, they have been shown to be robust against departures (8). These distributional assumptions, however, are not viewed as strictly valid in this study since there is good evidence in the literature that survival time due to certain cancers and other diseases is log normally distributed (30, 31, 32, 33). A linear rank procedure of the Prentice form, whose efficiency peaks under the lognormal distributional assumption, can be constructed (34), but this algorithm is not available at the present time; it will be included in the next analysis. The effect of this departure from the assumptions is considered mild. It should also be noted that these distributional assumptions cannot be checked since these match sets are small and the observations in the combined samples of all matched sets cannot be assumed to have a common distribution. Therefore, reliance must be placed on historical data to determine which linear rank procedure to use. The logrank and Wilcoxon procedures are used here because they are powerful and widely accepted in epidemiology and statistics.

4. Relative Risk Estimation

Two relative risk estimators are used in this analysis, a generalization of the Ejigou-McHugh estimator for one to many matched data (12) and the Mantel-Haenszel estimator for stratified data (14). The Ejigou-McHugh estimate was chosen because it allows full adjustment for the one-to-many year-of-birth matching in this study, it is asymptotically as efficient as the maximum likelihood estimator and it is noniterative. The Mantel-Haenszel estimate was chosen because of its ease of calculation, efficiency (35), and general acceptance. It's variance is estimated according to the advice of Anderson et al. (36). Recent work suggests that the variance of the Mantel-Haenszel statistic might be better estimated by a jack-knife procedure (37); this newer method will be carried out in the next mortality report.

The Ejigou-McHugh estimator in its published form is suitable only for 1 to R matched designs in which the number, R, of controls matched to each case is the same for all cases. Since the number of controls matched to each Ranch Hander is not the same for all Ranch Handers, the Ejigou-McHugh estimate and its variance was extended to a one-to-many matched design in which the number of comparisons is allowed to vary from case to case. Since this extension is unpublished it is stated in Appendix V for reference.

The extended estimate and its variance reduces to the Ejigou-McHugh estimate and variance when all matched sets contain an equal number of comparisons. It is asymptotically efficient and consistent and is noniterative.

The Ejigou-McHugh estimate and the Mantel-Haenszel estimate are based on the assumption that relative risk is constant across levels of the matching variable. Some indication that this assumption holds in this study when the data is grouped, by stratifying on year of birth, is furnished by likelihood ratio testing; there is no evidence in this study to suggest that relative

risk is not constant across levels of the matching variables when the event of interest is death from any cause. Therefore, the Ejigou-McHugh and Mantel-Haenszel estimates are appropriate for these data.

5. Indirect Standardization

With either an external or internal standard, the SMR is a good summary mortality index for comparing two or more populations, provided the product model, $P_{ij}=r_i p_j$, holds, where P_{ij} is the probability of death in stratum i of population j, r_i is a set of standard stratum specific rates and p_j characterizes the mortality of population j, i=1,2, ..., I, j=1,2, ..., J, (38, 13). If standard rates are known from some external source and if the product model holds, the best estimate of p_j is proportional to the SMR. If J=2, the product model holds, and if one of the two groups is used as the standard, the SMR estimates relative risk. In any case, any SMR summary of mortality data should be preceded by analytical and graphical tests of fit of the product model. Because one of the study groups was always used as the standard in these analyses, the test of fit of the product model was, equivalently, a test of constancy of relative risk across year of birth strata. The fit of the model was verified in each analysis. Further, a likelihood ratio test for equality of population was carried out as described by Gail (13). The results of both tests are summarized by their P-values in each application. The sample sizes in every application are large enough so that chi-square approximations hold; these analyses are, therefore, valid and appropriate.

The expected number of deaths in the SMR used in these analyses was calculated as $\sum n_{ij} r_i$, where n_{ij} is the number of subjects in the ith stratum of the jth population. The person-years SMR was not used here for two reasons. First, its validity as an estimator of relative risk is dependent upon the fit of the proportional hazards model for which an omnibus test is not currently available. Secondly, the person-years calculation is typically carried out from entry into follow-up (5); in this study, follow-up begins at first entry to Vietnam or Southeast Asia and these entry dates are being verified at this writing.

6. Comparing Observed Life Table Data with a Known Survival Curve

The procedure of Gail and Ware (17) is used in these analyses to compare Ranch Hand and comparison group survival data with published period life tables. The basic assumptions of this procedure are that death and censorship are independent competing risks and that the reference curve is a survival distribution for some external population. The test is of the form $\sum(o_j-e_j)/(\sum v_j)^{1/2}$, where o_j and e_j are observed and expected numbers of deaths in age interval j, and v_j is the variance of o_j-e_j. The statistic is not an omnibus goodness-of-fit test consistent against all alternatives to the null hypothesis that the observed sample comes from a known survival distribution. Rather, it has good power against proportional hazards alternatives or, more loosely, against alternatives for which the observed survival is better (or worse) in every interval than predicted by the known survival curve.

The independence of death and censorship assumption is well satisfied in these data, as discussed in Section 2 of this chapter. The life tables used in these analyses do not, however, represent the survival distribution of any population since they are period, not cohort, life tables. The appropriateness of this procedure is, therefore, dependent upon the extent to which these period life tables approximate the survival distribution of some relevant reference population. These period tables were used because the more appropriate cohort life tables were not available at the time of analysis.

Chapter VII

CONCLUSION

1. Introduction

The mortality analyses described in this report have not revealed any adverse death experience in the herbicide/dioxin exposed cohort. The results of the analyses, regardless of the source of the comparison data, were consistent: at this time, there is no indication that operation Ranch Hand personnel have experienced any increased mortality or any unusual patterns of death in time or by cause. They are not dying in increased numbers, at earlier ages, or by unexpected causes.

The fact that only a relatively small number of Ranch Hand deaths were available for analysis is reassuring in itself. However, the fact that adverse effects have not yet been detected does not imply that an effect will not become manifest at a future time or after covariate adjusted analyses. For this reason, further analyses are intended and mortality in the study population will be ascertained annually for the next 20 years.

A summary of the statistical techniques applied to each source of comparison data is presented in Table 42. It should be noted here that these analyses have been carried out without knowledge of covariate information, such as herbicide exposure, industrial chemical exposure, or other risk factors and that these analyses were carried out at a time when approximately 96% of Ranch Handers and their matched comparison subjects were still living. The data, therefore, must be viewed as preliminary to more definitive analyses, which will be performed over the next 20 years. Table 43 summarizes the results of the noncause specific analyses by source of the comparison data, and Table 44 presents the results of the cause specific analyses.

Table 42

SUMMARY OF STATISTICAL PROCEDURES USED IN ANALYSIS

Comparison Database	Internal Comparison Group	1978 U.S. White Males	1978 DoD Life Tables	West Point Class of 1956
Noncause Specific Analyses				
Logrank & Wilcoxon Procedures	+			+
Ejigou-McHugh Relative Risk	+			
Mantel-Haenszel Relative Risk	+			+
SMR/Breslow-Day Product Model	+			+
Gail-Ware Procedure		+	+	
Cause Specific Analyses				
Ejigou-McHugh Relative Risk	+			
Mantel-Haenszel Relative Risk	+			+

Procedure usage is indicated by a "+" symbol.

SUMMARY OF NONCAUSE SPECIFIC MORTALITY ANALYSES BY SOURCE OF COMPARISON DATA

	Internal Comparison Group	1978 US White Males[1]	1978 DoD Life Tables[1]	West Point Class of 1956[2]
Ranch Hand Group	$RH = C$ $RH_O = C_O$ $RH_E = C_E$ $RH_F = C_F$ $RH_G = C_G$	RH <<<US RH_O <<<US RH_E ≤US	RH_O <<<DoD_O $RH_E = DoD_E$	$RH_O = WP_O$
Comparison Group		C <<<US C_O <<<US C_E <<<US	$C_O < DoD_O$ C_E <<DoD_E	$C_O = WP_O$
Internal Occupational Group Specific	$RH_O \leq RH_E$ $RH_F \leq RH_G$ $C_O < C_E$ $C_F = C_G$			

=	P value[3] greater than .10
≤	P value equal to or less than .10
<	P value equal to or less than .05
<<	P value equal to or less than .01
<<<	P value equal to or less than .001

RH Ranch Hand Group
C Comparison Group
O Officers
E Enlisted
F Flying
G Ground

1 Validity of these comparisons is questionable (see Chapter 4)
2 Statistical inference is limited by small sample size
3 All P value symbols are based upon SMR and Gail-Ware analysis

Table 44

SUMMARY OF CAUSE SPECIFIC ANALYSES BY SOURCE OF COMPARISON DATA

RH Versus Internal Comparison	RH Versus West Point*
No significant difference in cause specific relative risks	No significant difference in cause specific relative risks

* Statistical inference is limited by small sample size

2. Internal Comparison Group

Based on these early results, there appears to be no significant difference between Ranch Handers and comparisons as regards mortality. This null finding holds for both cause specific and noncause specific comparisons. One within group comparison did yield a significant difference, however. The non-Black comparison officers are living significantly longer than the non-Black comparison enlisted personnel. This may reflect the underlying health care and socioeconomic differences between these two groups. Non-Black Ranch Hand officers also appear to be living longer than non-Black Ranch Hand enlisted personnel, but this finding cannot be viewed as significant, with a P-value of .142 (Table 17). This lack of significance in the Ranch Hand analysis might be attributed to the smaller group sizes within the Ranch Hand cohort in contrast to the comparison cohort.

3. External Comparisons

As outlined in the study protocol, considerable effort was expended in the selection of the study comparison group. While the chosen comparison group appeared closest to the Ranch Hand cohort except for herbicide exposure, it seemed appropriate to also contrast the Ranch Hand mortality experience to that of additional comparison groups. Three additional comparison data sets were then selected: mortality data from the West Point Class of 1956, the DoD Nondisability Retired Officer and Enlisted Life Tables for 1978, and the U.S. White Male Life Table, also for 1978. These data sets were chosen in a hierarchical fashion with the expectation that, in the absence of a herbicide effect, the Ranch Handers would have: 1) a mortality pattern comparable to the West Pointers, 2) a lower mortality than the DoD group due to the healthy worker effect, and 3) a still lower mortality than the U.S. male cohort due to healthy worker and military selection effects. These expectations were reassuringly fully realized with respect to overall mortality. Additionally, interesting officer-enlisted differentials emerged. As discussed below, these officer-enlisted differentials may have resulted from sample size effects or from covariable effects, potentially including herbicide exposure.

4. Power Considerations

The power limitations of this study, specifically regarding mortality from rare conditions, such as soft tissue sarcoma, were fully acknowledged and described in the protocol (Ref 1, page 67). For example, a fatal disease with an incidence of .001 would require an approximate risk of 4 for a power of 0.8.

Power calculations, while desirable for planning and study design, are also revealing at analysis. They are, however, sometimes difficult to carry out without further assumptions. The powers of the logrank and Wilcoxon tests

and the likelihood ratio tests in the SMR analyses are not calculable at this time due to the lack of appropriate methodology. The powers of the tests for cause specific mortality were calculated at the estimated relative risk. The values were low because the estimates of relative risk were close to unity and/or the data were sparse.

The null findings in this report are unlikely to have been observed by chance had the true group differences been substantial. For example, if the true overall relative risk were in fact equal to 2, a crude calculation gives a probability of .0007 of observing a relative risk smaller than the observed .964 (Table 7). This probability is less than .001 if the true relative risk is 1.5. These findings are, therefore, very likely reflective of a near overall equivalence between Ranch Handers and their matched comparisons. Finally, these unadjusted findings do not preclude the possibility of the emergence of significant differences after adjustment for risk factors.

5. Consistency Patterns

When the analysis of each external comparison data base is considered separately, the restrictions inherent in each source limit the strength of the inferences which can be made. However, when the results of all internal and external comparison data bases are considered in context, some patterns of consistency emerge. While some of these patterns may not have firm statistical underpinnings, they still may provide epidemiologic clues to the dynamics of the mortality process.

The Ranch Hand officers exhibit a very consistent and predictable pattern across all analyses. As shown in Table 43, their mortality is nearly the same as that of their most equivalent comparison groups (the matched comparison group officers and the West Point group). As the comparison groups become progressively less equivalent to the Ranch Hand group, the relative mortality of the Ranch Hand officers improves, presumably due to selection comparability (healthy worker effect, etc.). Their mortality is lower than that of their enlisted counterparts; however, this difference is not as striking as is the statistically significant comparable analysis between the matched comparison officers and the matched enlisted personnel.

Unfortunately, the cross-comparison trends for the enlisted Ranch Handers are not as clearcut. Their mortality is greater,though not significantly different from their matched comparisons. The enlisted comparison group had a highly significant underrepresentation of mortality against both the DoD and US life tables, whereas the Ranch Handers are equivalent to the DoD group and only marginally better than the 1978 US White males.

The consistent observation that the enlisted Ranch Handers appear to demonstrate less of a difference in relative mortality than do their matched comparisons is intriguing. This may reflect an actual increase in mortality due to herbicide exposure or some other factor, or it could be an artifact of small sample size created by the 1:5 matching or basic comparability problems as previously described. The inclusion of substantially more subjects in one group than another can have a profound effect on the significance level of a

statistical technique. Nevertheless, these observations are of interest, and will continue to be subjected to detailed analysis throughout the course of the follow-up study. This trend is consistent with self-perception of herbicide exposure held by many of the Ranch Hand group. Covariate analyses will be conducted, the herbicide exposure index will be applied to these data, and the effects of interaction will be assessed to determine whether the Ranch Hand enlisted findings are real or artifactual.

The next mortality assessment will include analyses by person-year of follow-up, adjusted for age in an effort to better address the issue of latency. As the number of deaths in the study population increases with the passage of time, all of the statistical approaches outlined in the protocol (1) will be applied to the data.

Appendix I

RANCH HAND II PRINCIPAL INVESTIGATORS COINVESTIGATORS, CONTRIBUTORS, AND MANAGEMENT PERSONNEL

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Appendix II

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Appendix III

MATCHING RESULTS IN THE MORTALITY POPULATION

The matching results are described here for the mortality population consisting of 1241 Ranch Hands, their 6171 matched mortality comparisons, and the six unmatched Ranch Hands. The matching procedure is described in the Protocol (Ref. 1, pages 23-26).

All study subjects were matched perfectly on job category. Three mismatches occurred on race because the recorded race designations for three study subjects were found to be incorrect at the LHA interview. These three subjects were comparisons, two were in the enlisted-other stratum (one was originally recorded as Black and was discovered to be non-Black, the other was originally recorded as non-Black and was discovered to be Black), and one was in the enlisted-flight engineer stratum (he was originally recorded as Black and was discovered to be non-Black).

Matching on date of birth was carried out by first expressing date of birth in months from 1 January 1900, to the nearest month; the result is termed month-of-birth. Six discrepancies occurred in matching on month-of-birth due to erroneous months-of-birth for one Ranch Hand and one comparison. These were discovered at the LHA interview. The Ranch Hand, in the non-Black enlisted-other stratum, was discovered to be 72 months older than was recorded prior to the matching. The comparison, in the non-Black officer-pilot stratum, was found to be 15 years younger than was originally recorded. The erroneous Ranch Hand month-of-birth put all five of his matched comparisons 12 months out of range since he was originally perfectly matched to all five mortality comparisons. The erroneous comparison month-of-birth put that comparison 119 months out of range. Given the very small number of mismatches on age and race relative to the number of subjects, their effect was assumed negligible.

The matching by month-of-birth, overall, and within each of the ten job and race categories within the mortality population is summarized in this Appendix. The column headed "Age Difference" lists absolute differences of months-of-birth of Ranch Hands and comparisons. The column headed "Number of Comparisons with RH younger (older)" gives, at each level of age difference, the number of comparisons within the level of age difference and older (younger) than the Ranch Hand to whom they are matched. The column headed "Total Count" gives the total numbers of comparisons having the absolute age differences with their matched Ranch Hand given in the first column; in "Total Percent", these counts are expressed as percentages of 6171. These are cumulated in the last two columns.

Appendix III

MATCH SUMMARY FOR THE MORTALITY POPULATION

Strata	Age Difference	Number of Comparisons with RH		Total		Cumulative	
		Younger	Older	Count	%	Total	%
Overall	0			4261	69.0	4261	69.0
	1-6	743	706	1449	23.5	5710	92.5
	7-12	77	102	179	2.9	5889	95.4
	13-18	40	36	76	1.2	5965	96.7
	19-24	22	22	44	0.7	6009	97.4
	25-30	12	19	31	0.5	6040	97.9
	31-36	16	14	30	0.5	6070	98.4
	37-42	10	19	29	0.5	6099	98.8
	43-48	9	13	22	0.4	6121	99.2
	49-54	13	7	20	0.3	6141	99.5
	55-60	17	7	24	0.4	6165	99.9
	72	0	5	5	0.1	6170	100.0
	179	0	1	1	0.0	6171	100.0
Officer-pilot	0			961	55.2	961	55.2
Non-Black	1-6	272	259	531	30.5	1492	85.8
	7-12	33	32	65	3.7	1557	89.5
	13-18	20	17	37	2.1	1594	91.6
	19-24	8	12	20	1.1	1614	92.8
	25-30	9	11	20	1.1	1634	93.9
	31-36	13	10	23	1.3	1657	95.2
	37-42	7	18	25	1.4	1682	96.7
	43-48	7	11	18	1.0	1700	97.7
	49-54	11	7	18	1.0	1718	98.7
	55-60	14	7	21	1.2	1739	99.9
	179	0	1	1	0.1	1740	100.0
Officer-Pilot	0			0	0.0	0	0.0
Black	1-6	3	0	3	23.1	3	23.1
	7-12	3	0	3	23.1	6	46.2
	31-36	0	1	1	7.7	7	53.9
	37-42	2	0	2	15.4	9	69.2
	43-48	1	0	1	7.7	10	76.9
	49-54	2	0	2	15.4	12	92.3
	55	1	0	1	7.7	13	100.0
Officer-	0			240	61.5	240	61.5
Navigator	1-6	74	70	144	36.9	384	98.5
Non-Black	7-12	0	6	6	1.5	390	100.0

Appendix III (Continued)
MATCH SUMMARY FOR THE MORTALITY POPULATION

Strata	Age Difference	Number of Comparisons with RH		Total		Cumulative	
		Younger	Older	Count	%	Total	%
Officer-Navigator Black	0			1	10.0	1	10.0
	1-6	0	1	1	10.0	2	20.0
	7-12	2	2	4	40.0	6	60.0
	13-18	0	1	1	10.0	7	70.0
	19-24	0	1	1	10.0	8	80.0
	25-30	0	1	1	10.0	9	90.0
	31-36	0	1	1	10.0	10	100.0
Officer-Other Non-Black	0			14	11.4	14	11.4
	1-6	38	57	95	77.2	109	88.6
	7-12	2	8	10	8.1	119	96.8
	13-18	1	1	2	1.6	121	98.4
	19-24	1	0	1	0.8	122	99.2
	25	0	1	1	0.8	123	100.0
Officer-Other Black	13-18	2	0	2	100.0	2	100.0
Enlisted-Flight Engineer Non-Black	0			516	55.2	516	55.2
	1-6	165	141	306	32.7	822	87.9
	7-12	29	34	63	6.7	885	94.7
	13-18	16	14	30	3.2	915	97.9
	19-24	0	7	7	0.7	922	98.6
	25-30	2	6	8	0.9	930	99.5
	31-36	2	1	3	0.3	933	99.8
	37-42	1	0	1	0.1	934	99.9
	46	1	0	1	0.1	935	100.0
Enlisted-Flight Engineer Black	0			10	13.3	10	13.3
	1-6	26	22	48	64.0	58	77.3
	7-12	7	5	12	16.0	70	93.3
	19-24	3	0	3	4.0	73	97.3
	55-58	2	0	2	2.7	75	100.0
Enlisted-Other Non-Black	0			2382	90.6	2382	90.6
	1-6	116	91	207	7.9	2589	98.5
	7-12	1	11	12	0.5	2601	99.0
	13-18	1	3	4	0.2	2605	99.1
	19-24	10	2	12	0.5	2617	99.6
	25-30	1	0	1	0.0	2618	99.6
	31-36	1	1	2	0.1	2620	99.7
	37-42	0	1	1	0.0	2621	99.7
	43-48	0	2	2	0.1	2623	99.8
	72	0	5	5	0.2	2628	100.0
Enlisted-Other Black	0			137	53.7	137	53.7
	1-6	49	65	114	44.7	251	98.4
	7-12	0	4	4	1.6	255	100.0

Appendix IV

YEAR OF BIRTH, OCCUPATIONAL AND RACE SPECIFIC MORTALITY

Job Category, Race	Birth Year	Ranch Hand At Risk	Ranch Hand Dead	Ranch Hand Death Rate	Comparison At Risk	Comparison Dead	Comparison Death Rate
Officer-Pilot, Non-Black	1915-19	8	3	.375	39	4	.103
	1920-24	31	0		155	13	.084
	1925-29	31	0		232	14	.060
	1930-34	113	3	.027	456	23	.050
	1935-39	66	3	.045	326	8	.025
	1940-44	60	1	.017	354	5	.014
	1945-49	40	2	.050	178	5	.028
	TOTAL	349	12	.034	1740	72	.041
Officer-Pilot, Black	1930-34	0	0		3	0	
	1935-39	1	0		4	0	
	1940-44	3	0		6	0	
	1945-49	2	0		0	0	
	TOTAL	6	0		13	0	
Officer-Navigator Non-Black	1925-29	9	0		47	3	.064
	1930-34	35	1	.029	163	7	.043
	1935-39	21	1	.048	105	3	.029
	1940-44	13	0		67	0	
	1945-49	2	0		8	0	
	TOTAL	80	2	.025	390	13	.033
Officer-Navigator Black	1930-34	1	0		6	0	
	1935-39	1	0		4	0	
	TOTAL	2	0		10	0	
Officer-Other, Non-Black	1910-14	1	0		2	0	
	1915-19	0	0		3	0	
	1920-24	1	0		6	0	
	1925-29	3	0		11	1	.091
	1930-34	2	0		12	1	.083
	1935-39	4	0		19	0	
	1940-44	13	1	.077	66	1	.015
	1945-49	1	0		4	0	
	TOTAL	25	1	.040	123	3	.024

Appendix IV (Continued)

Job Category, Race	Birth Year	Ranch Hand At Risk	Ranch Hand Dead	Death Rate	Comparison At Risk	Comparison Dead	Death Rate
Officer-Other, Black	1940-44	1	0		2	0	
	TOTAL	1	0		2	0	
Enlisted-Flt Eng Non-Black	1915-19	1	1	1.000	6	2	.333
	1920-24	4	0		20	4	.200
	1925-29	12	0		61	3	.049
	1930-34	64	3	.047	304	15	.049
	1935-39	48	2	.042	243	10	.041
	1940-44	41	0		211	7	.033
	1945-49	19	0		90	5	.056
	TOTAL	189	6	.032	935	46	.049
Enlisted-Flt Eng Black	1925-29	1	0		10	1	.100
	1930-34	6	1	.167	34	5	.150
	1935-39	5	0		16	1	.063
	1940-44	3	1	.333	15	2	.133
	TOTAL	15	2	.133	75	9	.120
Enlisted-Other Non-Black	1905- 9	0	0		2	0	
	1910-14	4	2	.500	10	2	.200
	1915-19	8	0		48	5	.104
	1920-24	12	3	.250	60	7	.117
	1925-29	28	2	.071	140	18	.129
	1930-34	76	6	.079	376	14	.037
	1935-39	52	1	.019	263	8	.030
	1940-44	67	2	.030	340	7	.021
	1945-49	270	9	.033	1333	36	.027
	1950-54	11	0		56	0	
	TOTAL	528	25	.047	2628	97	.037
Enlisted-Other Black	1930-34	7	1	.143	35	2	.057
	1935-39	9	0		40	3	.075
	1940-44	7	0		35	1	.029
	1945-49	29	1	.034	145	4	.028
	TOTAL	52	2	.038	255	10	.039

Appendix V

THE EXTENDED EJIGOU-McHUGH RELATIVE RISK ESTIMATOR

Let R_k, k=1,2, ..., K, denote the distinct numbers of comparisons matched to the cases and let n_k denote the number of matched sets with exactly R_k comparisons. A matched set is defined as the case and his matched comparisons. Let $n=n_1+n_2+ \ldots +n_K$ denote the total number of matched sets.

Define $Z_{k,i,T}$, k=1,2, ...,K, i=0,1, by

$Z_{k,0,T}$ = the number of matched sets, among those having exactly R_k comparisons, in which the case is alive and exactly T of the R_k comparisons have died, T=1,2, ..., R_k

$Z_{k,1,T}$ = the number of matched sets, among those having exactly R_k comparisons in which the case has died and exactly T of the R_k comparisons have died, T=0,1,2, ..., R_k-1.

The extended estimate, ψ, is given by

$$\psi = \frac{\sum_{k=1}^{K} \sum_{T=1}^{R_k} Z_{k,0,T} Z_{k,1,T-1} / (Z_{k,0,T} + Z_{k,1,T-1})}{\sum_{k=1}^{K} \sum_{T=1}^{R_k} T Z^2_{k,0,T} / (R_k - T + 1)(Z_{k,0,T} + Z_{k,1,T-1})}$$

and its variance is estimated by

$$\sigma^2 = \frac{\psi}{\sum_{k=1}^{K} \sum_{T=1}^{R_k} Z_{k,0,T} / [\psi + (R_k - T + 1)/T]}.$$

Since K is finite, this estimate has the same distributional properties as the Ejigou-McHugh estimator; it is asymptotically efficient and unbiased. The underlying assumptions used in its derivation are that the disease under study is of low incidence and that relative risk is constant over the levels of the matching variables. The Ejigou-McHugh estimate and the above extension are equivalent in asymptotic efficiency to maximum likelihood estimation (12).

Appendix VI

Figure 4
SURVIVAL CURVE ESTIMATE AND 95% CONFIDENCE BANDS
FOR POOLED RANCH HANDERS

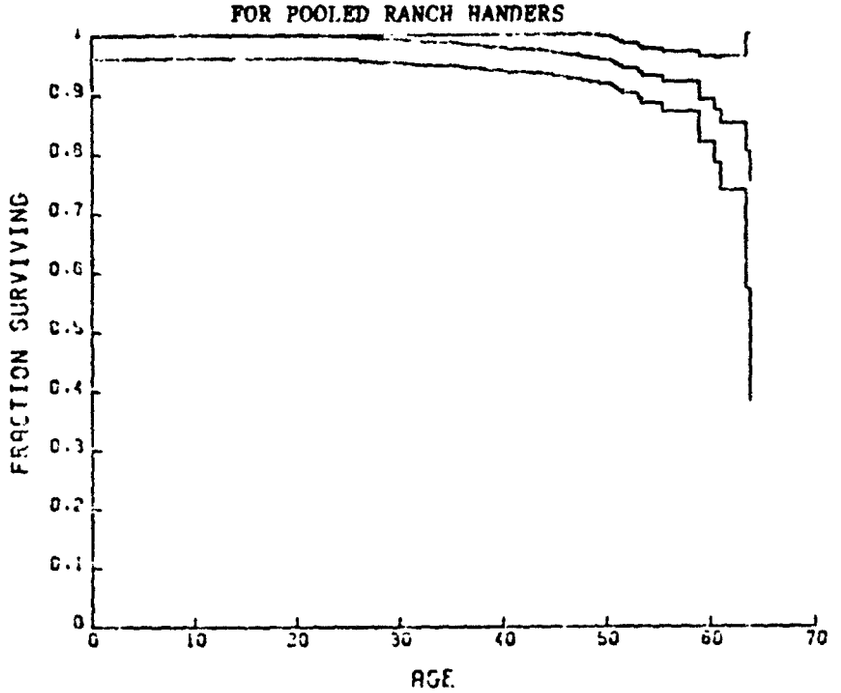


Figure 5
SURVIVAL CURVE ESTIMATE AND 95% CONFIDENCE BANDS
FOR POOLED COMPARISONS

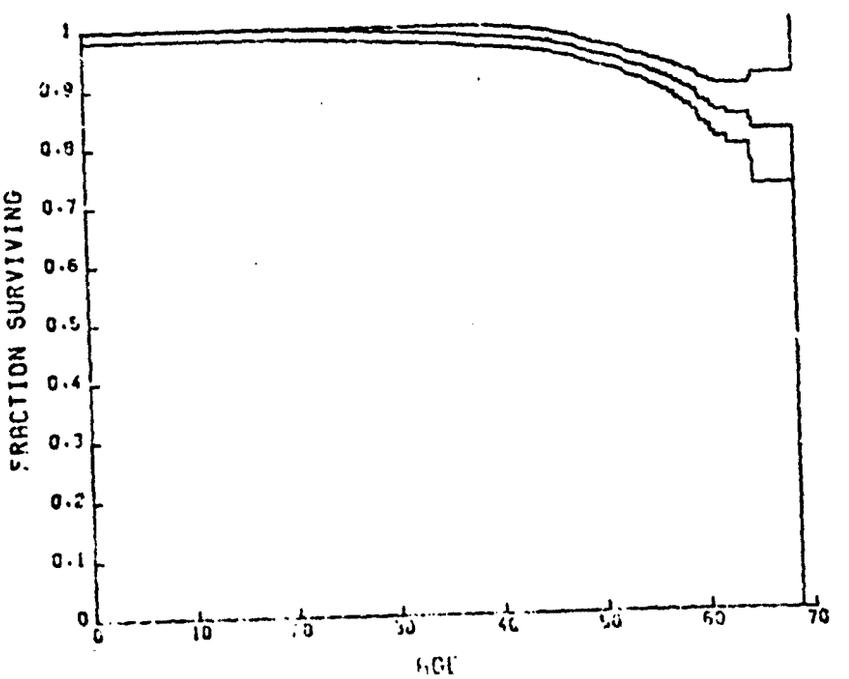


Figure 6
SURVIVAL CURVE ESTIMATE AND 95% CONFIDENCE BANDS
FOR RANCH HAND OFFICERS

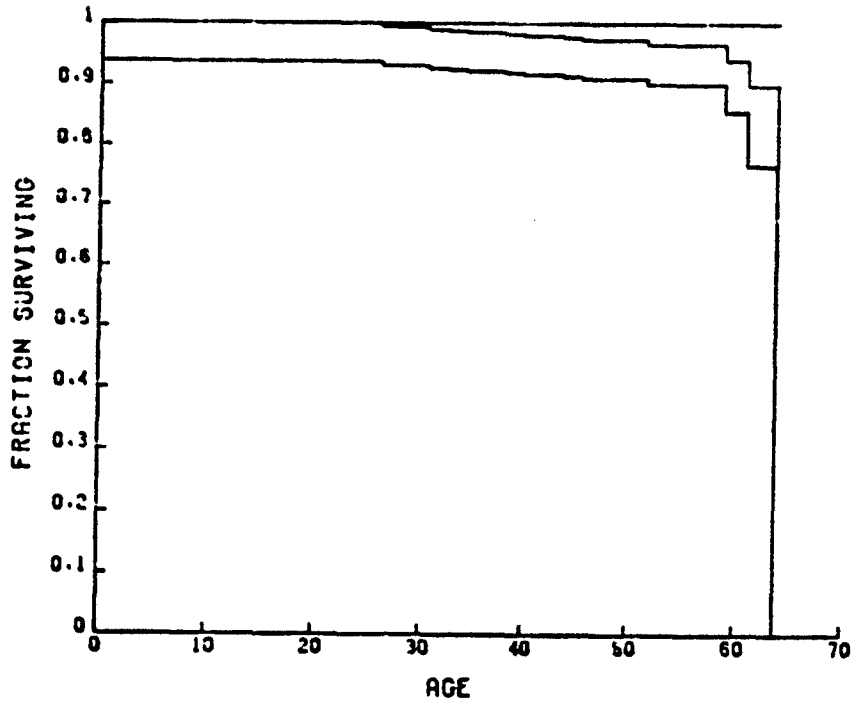


Figure 7
SURVIVAL CURVE ESTIMATE AND 95% CONFIDENCE BANDS
FOR COMPARISON OFFICERS

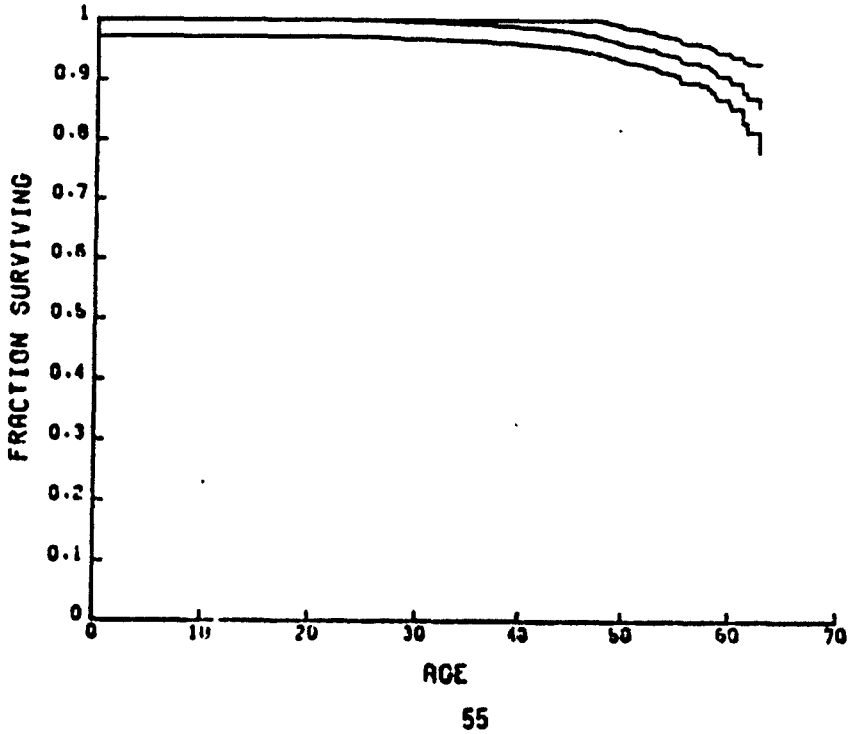


Figure 8

SURVIVAL CURVE ESTIMATE AND 95% CONFIDENCE BANDS
FOR RANCH HAND ENLISTED PERSONNEL

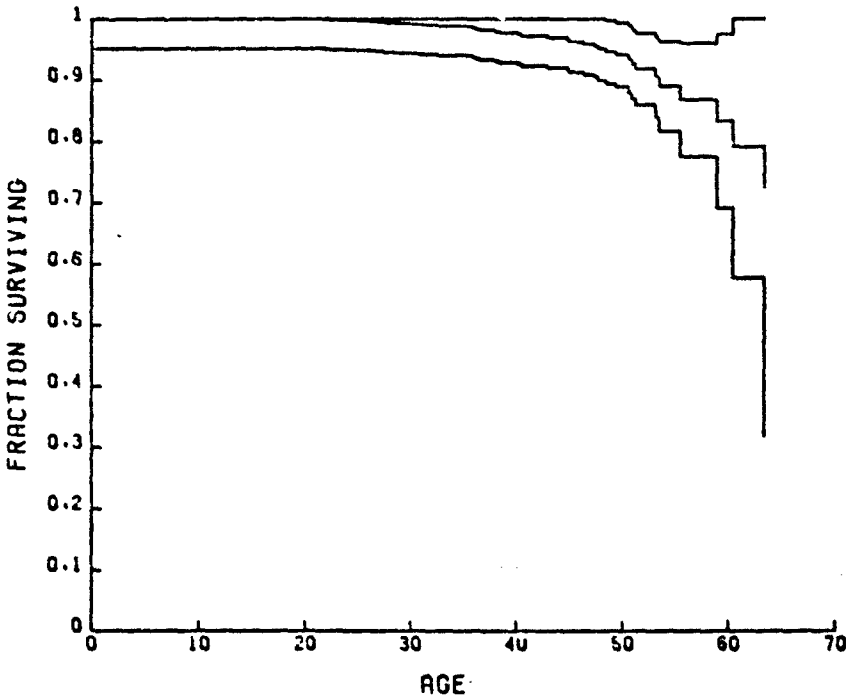


Figure 9

SURVIVAL CURVE ESTIMATE AND 95% CONFIDENCE BANDS
FOR COMPARISON ENLISTED PERSONNEL

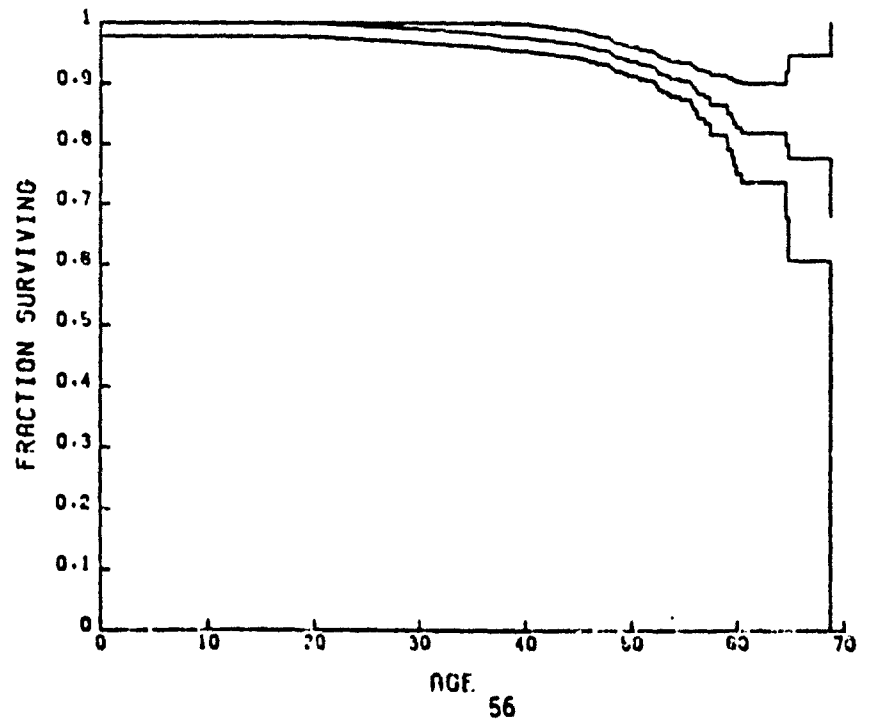


Figure 10

SURVIVAL CURVE ESTIMATE AND 95% CONFIDENCE BANDS
FOR RANCH HAND FLYING PERSONNEL

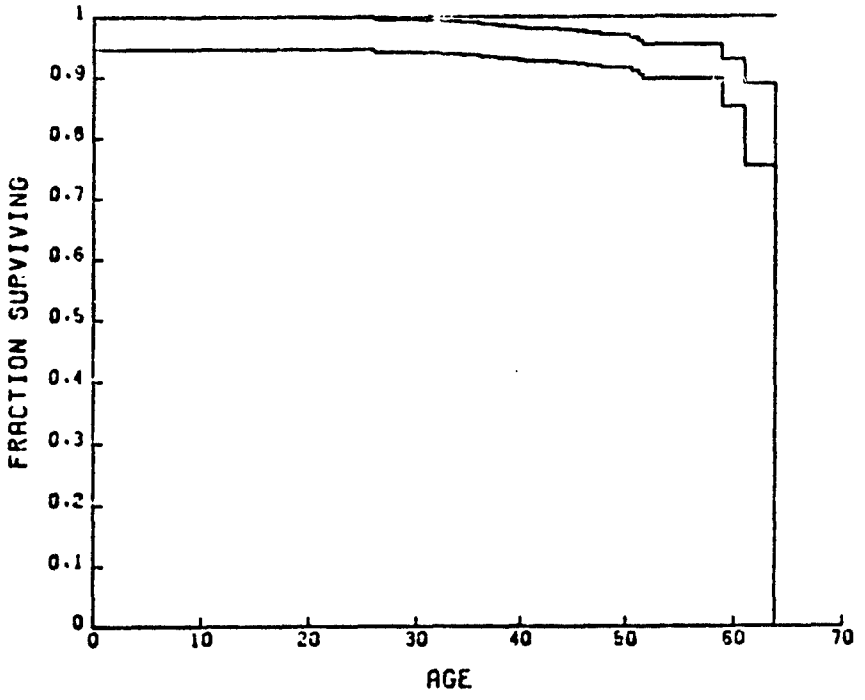


Figure 11

SURVIVAL CURVE ESTIMATE AND 95% CONFIDENCE BANDS
FOR COMPARISON FLYING PERSONNEL

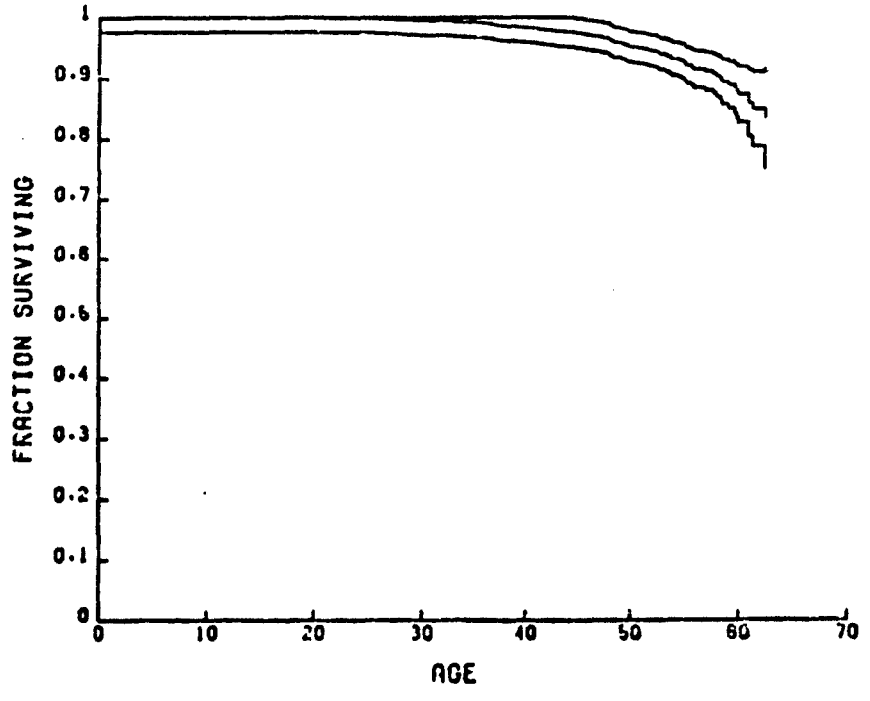


Figure 12

SURVIVAL CURVE ESTIMATE AND 95% CONFIDENCE BANDS
FOR RANCH HAND GROUND PERSONNEL

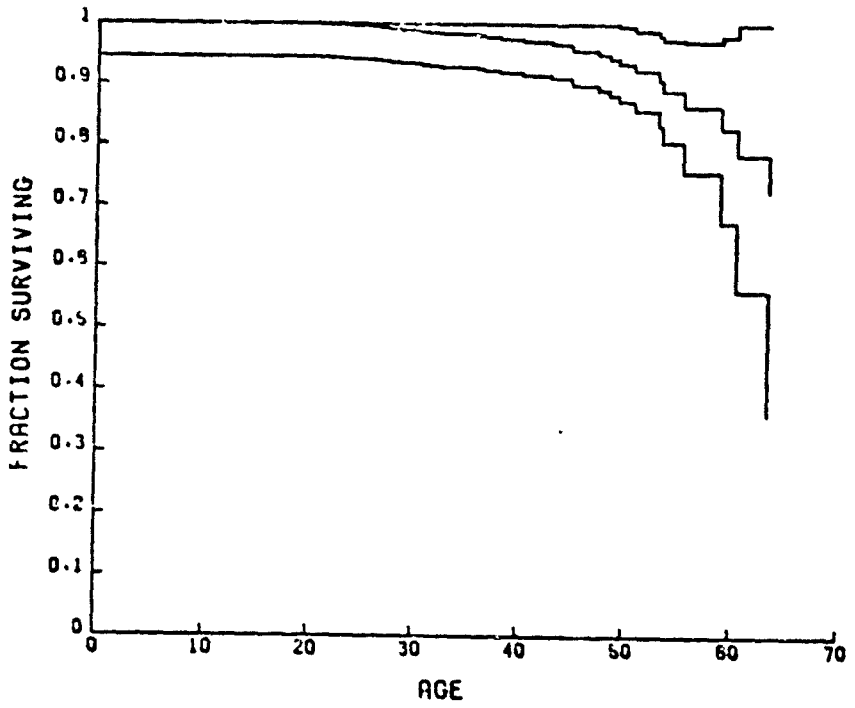
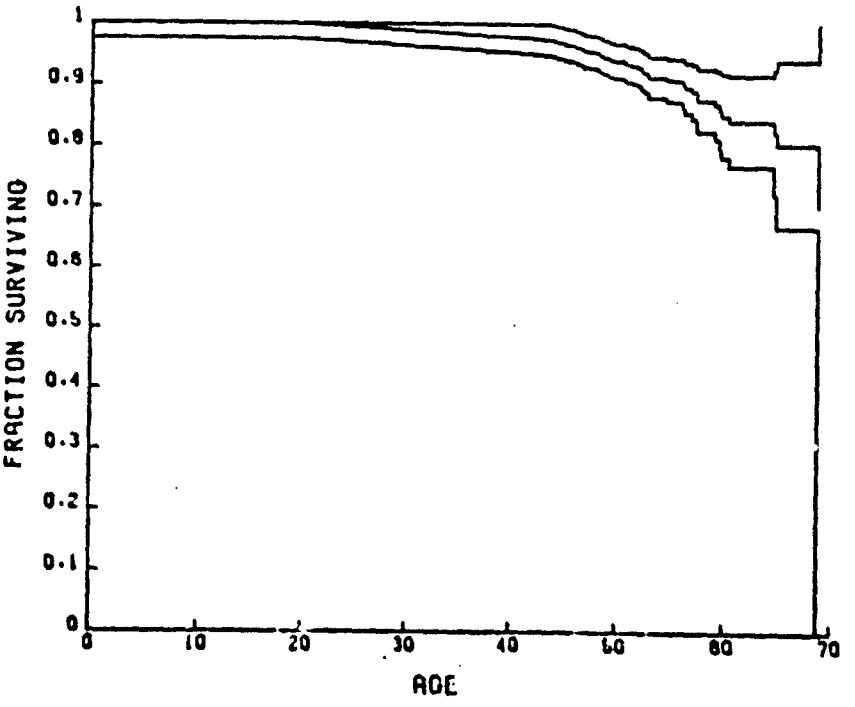


Figure 13

SURVIVAL CURVE ESTIMATE AND 95% CONFIDENCE BANDS
FOR COMPARISON GROUND PERSONNEL



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